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Synthesis and application of reactive BODIPY dyes

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Doctoral Thesis
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Samenvatting

De boordifluoridecomplexen van dipyrrineliganden zijn sterk gekleurde stoffen, die vaak intens fluoresceren. Ze hebben erg aantrekkelijke eigenschappen, zoals hoge kwantumrendementen voor fluorescentie, smalle absorptie- en emissiebanden met een lage solventafhankelijkheid en een hoge stabiliteit. Hierdoor worden ze momenteel gebruikt in biomedisch onderzoek en in nieuwe materialen, waar ze vooral bekend zijn onder hun handelsnaam BODIPY.
Mede verantwoordelijk voor hun populariteit is de mogelijkheid om door functionalisatie van deze fluoroforen hun spectrale eigenschappen aan te passen, of nieuwe functionele groepen in te voeren.
In het eerste deel van dit onderzoek worden de synthese en de eigenschappen van mono- gehalogeneerde BODIPY's beschreven. Door een keuze te maken uit selectief gefunctionaliseerde bouwstenen, kunnen de eigenschappen van de resulterende kleurstoffen gecontroleerd worden. De BODIPY's vertonen een excellente reactiviteit, en de reacties met nucleofielen en in transitiemetaalgekatalyseerde koppelingen worden beschreven. Uit een studie van de spectroscopische eigenschappen van de bekomen producten, kon een relatie bekomen worden tussen de structuur en de fluorescentie eigenschappen.
Naast de gehalogeneerde systemen, werden ook verscheidene thioëthersystemen bereid. De thioëthers vertonen een soortgelijke reactiviteit, maar zijn hierin volledig orthogonaal aan gehalogeneerde systemen. Deze orthogonaliteit wordt toegepast in hybride systemen, met zowel een halogeen- als een zwavelsubstituent, welke met volledige selectiviteit gesubstitueerd kunnen worden.
Deze reactiviteit van gehalogeneerde en gethioleerde systemen werd doorgevoerd naar 1,7-digesubstitueerde systemen. Dit zijn de enige posities waarvan nog niets bekend was betreffende reactiviteit en spectrale eigenschappen. Hoewel de reactiviteit lager ligt dan bij de eerder onderzochte systemen, konden zowel transitiemetaalgekatalyseerde reacties als nucleofiele aromatische substitutie ontwikkeld worden.
Verder werd een nieuwe benadering tot rotationeel ingeperkte BODIPY-kleurstoffen ontdekt. Deze ingeperkte systemen vertonen vaak roodverschoven spectra in combinatie met hoge kwantumrendementen, maar zijn erg moeilijk te bereiden. Door gebruik te maken van een palladiumgekatalyseerde oxidatieve ringvorming, werden zulke systemen bereid in een tweestaps- synthese. De spectrale eigenschappen van deze producten tonen dat de invoering van ingeperkte ringen inderdaad leidt tot verbeterde eigenschappen.
Een belangrijke verwezenlijking is de directe substitutie van het α-waterstofatoom op ongesubstitueerde BODIPY-fluoroforen. Hierdoor kunnen functionele groepen ingevoerd worden op systemen zonder reactieve

groepen, en dit in hoge rendementen.
De reactieve systemen die ontwikkeld werden gedurende het onderzoek zijn gebruikt in enkele toepassingen die hun uitzonderlijk potentieel moeten onderstrepen, zoals sensoren met een ratiometrische respons voor metaalionen, of in conjugaten met een peptide voor gebruik in fotodynamische therapie.

Abstract

Boron dipyrrins are highly coloured compounds that often show intense fluorescence. They display many highly desirable properties, such as high quantum yields of fluorescence, small absorption and emission bandwidths and a high stability. Also, these properties are mostly independent of solvent polarity. Because of these traits, they are currently used in biomedical research, and in the quest for novel materials, where they are known under their trade name BODIPY. Through functionalisation of the dye, it is possible to adapt the physicochemical and spectral properties of the dyes. This versatility is partially responsible for their current popularity.

In the first part of the research, synthesis and properties of monohalogenated BODIPY fluorophores are described. Via a careful choice of selectively functionalized building blocks, one can fully determine the properties of the resulting dyes. The BODIPYs show an excellent reactivity, in both nucleophilic aromatic substitution and palladium catalyzed coupling reactions. A spectroscopic study allowed the establishment of a structure-property relationship.

The reactivity of these systems was even further improved by the preparation and selective substitution of sulphur analogues and sulphur-halogen hybrids.

A general condensation route is described towards 1,7-disubstituted BODIPY dyes, substituting positions that were neglected up to now. The reactivity is somewhat lowered, when compared to previously reported systems, but nevertheless substituted products could be obtained.

Through a palladium catalyzed ring annulation reaction, novel restricted BODIPY dyes with red-shifted absorption and emission could be obtained in a simple two step sequence. From a detailed study it was shown that their properties indeed improve upon rigidification.

A major accomplishment of this research is the selective substitution of hydrogen in an oxidative process. As this process uses standard, unsubstituted dyes, no tedious functional group introduction is needed to reach reactive BODIPY fluorophores.

The reactive systems developed during the research were used in a few proof of concept applications, such as sensors with a ratiometric response to metal ions, and conjugates of a peptide with a BODIPY dye for use in photodynamic therapy.

List of Abbreviations

AIBN: Azobisisobutyronitrile, or 2,2′-Azobis(2-methylpropionitrile)
a-PET: Acceptor Photoinduced electron transfer
BODIPY: boron dipyrrin, 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene
CAN: Ceric ammonium nitrate
CSD: Cambridge Structural Database
CuMeSal: Copper(I) 3-methylsalicylate
CuTC: Copper(I) thiophene-2-carboxylate
DAMBOO: 8-Diaminophenyl-BOdipy-4-(di-*O*-methyl)
DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM: Dichloromethane
DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHBI: 4,5-dihydro-1H-benzo[g]indole
DIBALH: Diisobutylaluminum hydride
DIPEA: *N,N*-Diisopropylethylamine, or Hünig's base
DMA: *N,N*-dimethylacetamide
DMF: *N,N*-dimethylformamide
d-PET: Donor Photoinduced electron transfer
DTT: Dithiothreitol, Cleland's reagent
EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
EWG: Electron withdrawing group
Fwhm: Full width at half maximum
HOBT: 1-Hydroxybenzotriazole
HOMO: Highest occupied molecular orbital
HPLC: High Performance Liquid Chromatography
LG: Leaving group
LUMO: Lowest unoccupied molecular orbital
MW: Microwave
NEMP: *N*-Ethyl-morpholine
NBS: *N*-bromosuccinimide
NCS: *N*-chlorosuccinimide
NIR: Near Infrared (light)
NLS: Nucleus Locating Sequence
NMR: Nuclear Magnetic Resonance
NMP: *N*-Methyl-2-pyrrolidone
ONSH: Oxidative nucleophilic substitution of hydrogen
PET: Photoinduced electron transfer
PDT: Photodynamic Therapy
Pin: Pinacolate
S_NAr: Nucleophilic aromatic substitution
TFA: Trifluoroacetic acid
TFP: tri(2-furyl) phosphine
TIPSA: triisopropylsilylacetylene

TIPS: triisopropylsilyl
THF: tetrahydrofuran
TMSA: trimethylsilylacetylene
TMS: trimethylsilyl
UV-Vis: Ultra Violet-Visible light
VNS: Vicarious nucleophilic substitution (of hydrogen)

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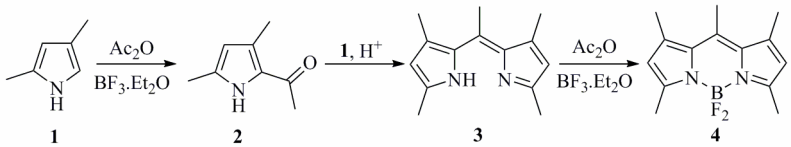
1. Introduction

1.1. Boron difluoride dyes

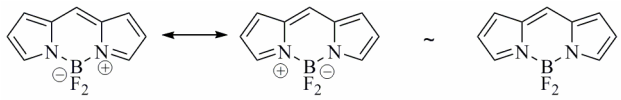
1.1.1. Discovery and structure

In 1968, Treibs and Kreuzer noticed that the acylation of 2,4-dimethylpyrrole **1**, with acetic anhydride and boron trifluoride as Lewis acid catalyst, resulted in the formation of a highly fluorescent compound **4**, rather than the desired acylated pyrroles **2**.[1] The compound arose from an acid catalyzed condensation of pyrroles **1** and **2** to dipyrrin **3**, followed by complexation with a boron difluoride unit to the dye **4** (Scheme 1).



Scheme 1. First synthesis of a boron dipyrrin dye by Treibs and Kreuzer

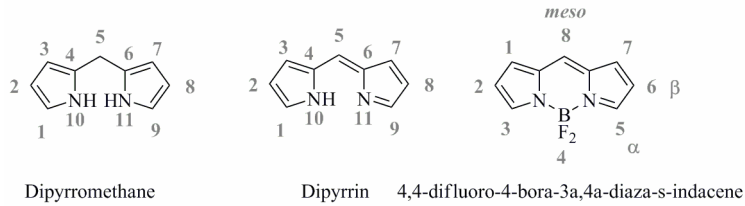
These compounds, based on the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene core (hereafter abbreviated to its brand name BODIPY) are generally dyes that absorb light in the visible range, and are often fluorescent with high quantum yields of fluorescence.[2] Their absorbance and emittance profiles tend to be relatively sharp and are only slightly Stokes shifted. They are uncharged, and their characteristics are mostly independent of solvent polarity. The complexes are stable in physiological pH-range, only decomposing in strong acidic and basic conditions.[3] These desirable properties combine with a low toxicity,[4] to make them excellent probes for use in biological systems and novel materials.



Scheme 2. The two equivalent resonance structures are usually depicted as an uncharged form

1 A. Treibs, F. Kreuzer, *Justus Liebigs Ann. Chem.*, **1968**, 718, 208.
2 A. Loudet, K. Burgess, *Chem. Rev.*, **2007**, 107, 4891.
3 R. Haugland, *Handbook of Fluorescent Probes and Research Chemicals*, 10th ed.; Molecular Probes: Eugene, OR, **2005**.
4 R. Alford, H. Simpson, J. Duberman, G. Hill, M. Ogawa, C. Regino, H. Kobayashi, P. Choyke, *Molecular Imaging*, **2009**, 8, 341.

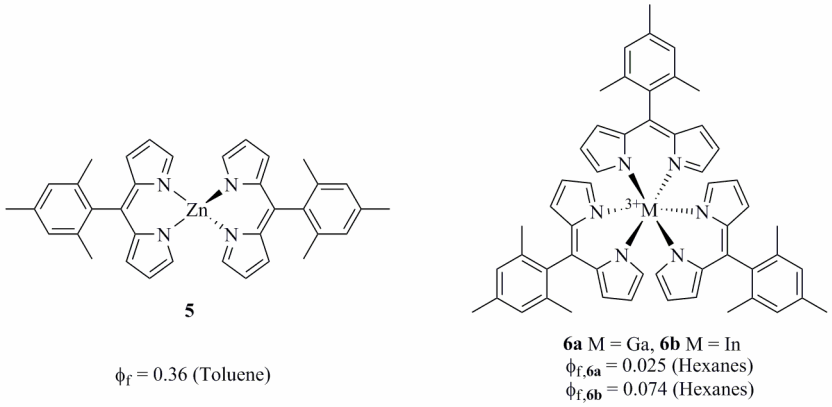
The numbering of the related dipyrromethane and dipyrrin systems is depicted in Scheme 3.[5] While for a dipyrromethane and a dipyrrin these are identical, the boron complex is somewhat different. In all three cases, the central carbon is referred to as the *meso* position, stemming from porphyrin nomenclature. Also, the positions adjacent to the nitrogen atoms are called α-positions, indicating the peculiar reactivity of this position in pyrroles, while the others are β-positions.



Scheme 3. Structure and IUPAC numbering of a dipyrromethane, a dipyrrin and a boron dipyrrin

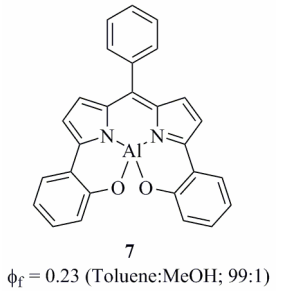
Of similar complexes reported with elements other than boron, only a few are fluorescent (Scheme 4).[5] The quenching of fluorescence with metals is believed to occur through electron transfer of the dipyrrin complex in the excited state. As an example of these non boron dyes, the zinc complex **5** has a fluorescence quantum yield of 0.36 in toluene.[6] The gallium **6a** and indium **6b** complexes are also slightly fluorescent.[7] The use of *meso* mesityl substituents in these complexes is imperative for the blocking of non radiative decay of the excited state through rotation.

5 T. Wood, A. Thompson, *Chem. Rev.*, **2007**, 107, 1831.
6 (a) L. Yu, K. Muthukumaran, I. Sazanovich, C. Kirmaier, E. Hindin, J. Diers, P. Boyle, D. Bocian, D. Holten, J. Lindsey, *Inorg. Chem*., **2003**, 42, 6629; (b) I. Sazanovich, C. Kirmaier, E. Hindin, L. Yu, D. Bocian, J. Lindsey, D. Holten, *J. Am. Chem. Soc*., **2004**, 126, 2664.
7 V. Thoi, J. Stork, D. Magde, S. Cohen, *Inorg. Chem.*, **2006**, 45, 10688.



Scheme 4. Fluorescent dipyrrin complexes with metals other than boron

The original report of Treibs and Kreuzer also mentions strong fluorescence for aluminium complexes, but as the compounds are highly water sensitive, a full study of their properties has not yet been published.[1] Recently, chelation of the aluminium centre with neighbouring phenolate ligands has led to a few stable aluminium dipyrrins **7**, which display moderate quantum yields of fluorescence.[8]



Scheme 5. A fluorescent aluminium dipyrrin

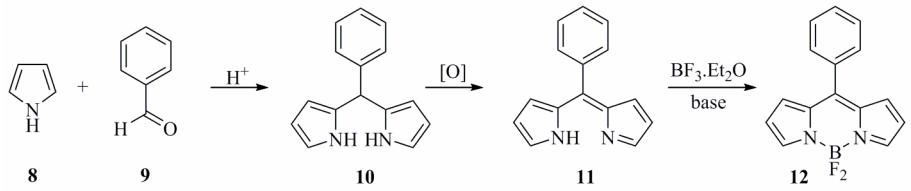
1.1.2. Synthetic routes towards the BODIPY core

There are two distinct synthetic approaches to the borondipyrromethene core, and they are both based on chemistry well known from porphyrin research.[5]

The acid catalyzed condensation of aldehydes **9** with pyrrole **8** affords dipyrromethanes **10 (**Scheme 6**)**. These reactions are normally carried out in

8 C. Ikeda, S. Ueda, T. Nabeshima, *Chem. Commun.***, 2009**, 2544.

pyrrole as the solvent to prevent polymerization.[9] Dipyrromethanes **10** are unstable compounds, and as they are sensitive to light, air and acid, best used immediately after preparation. Oxidation of the dipyrromethane **10** yields a dipyrromethene, or dipyrrin **11** (Scheme 4). This oxidation can be carried out with DDQ or *p*-chloranil, the latter providing milder reaction conditions. Also, there are only a few examples where the aldehyde is not an aromatic aldehyde, as the oxidation tends to fail in other cases.[6] Subjecting the dipyrrin to base and boron trifluoride etherate affords the borondifluoride complex **12** in high yield.



Scheme 6. Catalyzed condensation of aromatic aldehydes with pyrrole in the route to boron dipyrrins

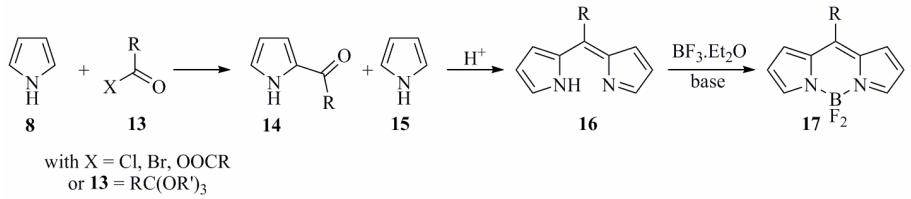
A somewhat different route uses the condensation of pyrrole **8** with an acylium equivalent **13** (Scheme 7). The intermediate acylpyrrole **14** is usually not isolated, as it can react under acidic conditions with an excess of pyrrole to form a dipyrrin **16**. The acylium equivalent can be an acid chloride,[10] anhydride[11] or an orthoester.[12] This approach allows for the synthesis of asymmetric dipyrrins, as an isolated acylpyrrole can be combined with a second pyrrole moiety **15** in an acidic condensation. Again, application of an excess of base and boron trifluoride etherate yields the BODIPY dye **17**.

9 (a) P. Rao, S. Dhanalekshmi, B. Littler, J. Lindsey, *J. Org. Chem*., **2000**, 65, 7323; (b) C. Lee, J. Lindsey, *Tetrahedron*, **1994**, 50, 11427; (c) B. Littler, M. Miller, C. Hung, R. Wagner, D. O'Shea, P. Boyle, J. Lindsey, *J. Org. Chem*., **1999**, 64, 1391.

10 (a) M. Shah, K. Thangaraj, M. Soong, M. Wolford, J. Boyer, I. Politzer, T. Pavlopoulos, *Heteroat. Chem.*, **1990**, 1, 389; (b) J. Boyer, A. Haag, G. Sathyamoorthi, M. Soong, K. Thangaraj, T. Pavlopoulos, *Heteroat. Chem.*, **1993**, 4, 39.

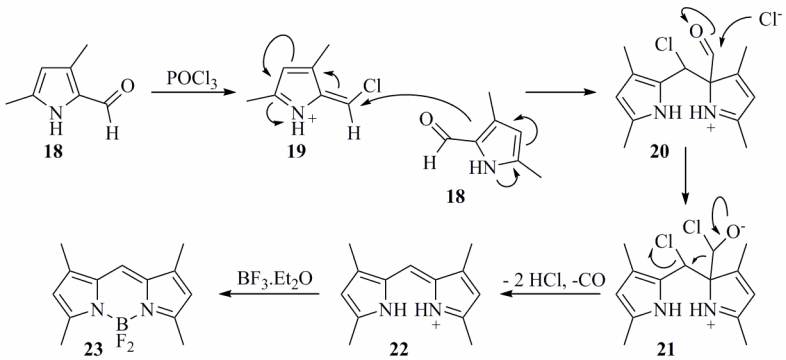
11 Z. Li, E. Mintzer, R. Bittman, *J. Org. Chem*., **2006**, 71, 1718.

12 V. Yakubovskyi, M. Shandura, P. Mykola, Y. Kovtun, *Eur. J. Org. Chem.*, **2009**, 19, 3237.



Scheme 7. Acid catalyzed condensation of an acylpyrrole with another pyrrole moiety to form dipyrrins and BODIPY dyes

An interesting alternative to the condensation of an acylated pyrrole was described by Burgess et al.[13] Their serendipitous discovery that the second pyrrole equivalent is not always needed, and phosphorus oxychloride is capable of condensing pyrrole-2-carbaldehyde **18** with itself, deserves a closer look. The mechanism postulated for this condensation is based on the fact that a carbon needs to disappear, and probably does so in the form of carbon monoxide (Scheme 8). Phosphorus oxychloride substitutes the aldehyde oxygen, resulting in a chlorinated azafulvene **19**, which is attacked by a second pyrrole aldehyde **18**. Subsequent nucleophilic attack by a chloride anion, followed by decomposition of the unstable intermediate yields a dipyrrin **22**. The dipyrrin can undergo complexation in a standard fashion to **23**. Obviously, this mechanism is only possible in the case of 5-substituted pyrrole aldehydes, but the yields are generally exceptionally high, arise from a one pot procedure and require little purification.



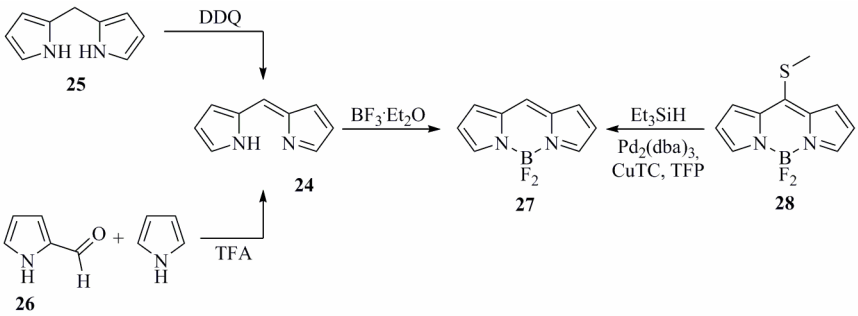
Scheme 8. Proposed mechanism of the decarboxylative condensation of pyrrole carbaldehydes mediated by $POCl_3$

The parent BODIPY system **27** was not synthesized until 2009, when three different groups simultaneously reported their findings (Scheme 9).[14] The

13 L. Wu, K. Burgess, *Chem. Commun*., **2008**, 40, 4933.

14 (a) A. Schmitt, B. Hinkeldey, M. Wild, G. Jung, *J. Fluoresc*., **2009**, 19, 755; (b) K. Tram, H. Yan, H. Jenkins, S. Vassiliev, D. Bruce, *Dyes Pigm.*, **2009**, 82, 392;

problems met in synthesizing the unsubstituted BODIPY dye **27** have been related to the instability of the intermediate dipyrrin **24**, which decomposes when brought at temperatures over -40°C.[15] Nonetheless, this approach was followed by Tram et al., who prepared the compound in 5-10% yield by carrying out the reactions at -78°C. Schmitt and co-workers reported the use of a trifluoroacetic acid mediated McDonald type condensation from pyrrole-2-carbaldehyde **26** and pyrrole to the unsubstituted dipyrrin. Another approach came from Peña-Cabrera, reducing a thiomethyl substituted BODIPY dye **28**. The unsubstituted dye **27** is highly fluorescent, with a fluorescence quantum efficiency of 90% in water.



Scheme 9. Syntheses of unsubstituted BODIPY

It is also worth mentioning that 8-aza analogues exist.[16] These aza-BODIPY dyes are prepared by complexing the aza-dipyrrins, which are in turn prepared by one pot condensation or via intermediate nitrosopyrroles.[17] The nitromethane adducts of chalcones **29** condense at elevated temperatures with a nitrogen source to form pyrroles **30**, which are partially nitrosated to **32** in the reaction mixture (Scheme 10). A second condensation of these two pyrrole moieties then results in the formation of an aza-dipyrrin **31**. The deep blue aza-dipyrrins have been known since 1932,[17] but the complexation to the aza-BODIPY **33** was not reported until 2004.[16] In the same study, optimized reaction conditions to the aza-dipyrrins were found, and carrying out the reaction in butanol leads to an efficient precipitation of the aza-dipyrrin **31**.[16b] Unfortunately, these dyes can only be prepared from heavily

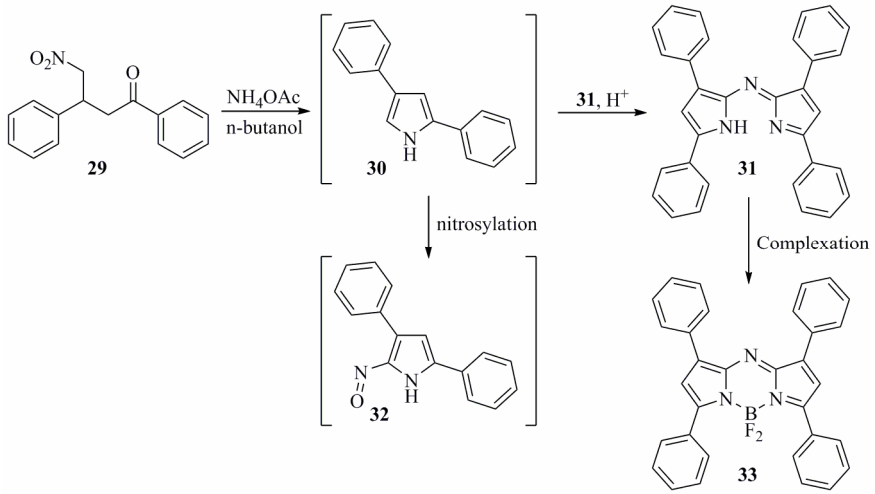
(c) I. Arroyo, R. Hu, G. Merino, B. Zhong Tang, E. Peña-Cabrera, *J. Org. Chem.*, **2009**, 74, 5719.

15 J. Van Koeveringe, J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, **1977**, 96, 55.

16 (a) J. Killoran, L. Allen, J. Gallagher, W. Gallagher, D. O'Shea, *Chem. Commun.*, **2002**, 1862; (b) A. Gorman, J. Killoran, C. O'Shea, T. Kenna, W. Gallagher, D. O'Shea, *J. Am. Chem. Soc*., **2004**, 126, 10619.

17 (a) M. Rogers, *J. Chem. Soc.*, **1943**, 590; (b) W. Davies, M. Rogers, *J. Chem. Soc.*, **1944**, 126; (c) E. Knott, *J. Chem. Soc.*, **1947**, 1196.

substituted pyrroles, such as 2,4-diarylpyrroles or ring annelated pyrroles.[18] Several groups have placed considerable effort in the synthesis of the alkyl analogues and less densely substituted systems, but without any success.

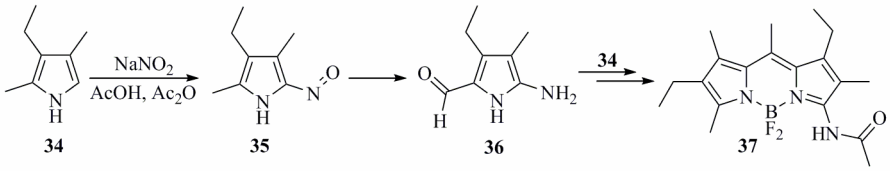


Scheme 10. Synthesis of aza-BODIPY dyes through a one pot condensation sequence

As a matter of fact, in 2007, the group of Amat-Guerri published its results on an unexpected redox reaction of the intermediate nitrosopyrroles **35**, leading to amide substituted BODIPY dyes **37** rather than aza-BODIPY fluorophores (Scheme 11).[19] Mass spectral evidence shows that, under the given reaction conditions, the nitrosyl group can oxidize the α-methyl group of pyrrole to form the aldehyde. Concomitantly, the nitrosyl is reduced to the amine. The newly formed aldehyde then condenses in a classical fashion with another pyrrole, and the final product is an acylated BODIPY **37**. The reaction is only possible with fully substituted pyrroles such as kryptopyrrole **34**, as other pyrroles result in total decomposition. This small scope has seriously reduced the use of the aza-BODIPY dyes.

18 (a) W. Zhao, E. Carreira, *Angew. Chem., Int. Ed.*, **2005**, 44, 1677; (b) W. Zhao, E. Carreira, *Chemistry*, **2006**, 12, 7254.

19 M. Liras, J. Prieto, M. Pintado-Sierra, F. Arbeloa, I. Garcia-Moreno, A. Costela, L. Infantes, R. Sastre, F. Amat-Guerri, *Org. Let.*, **2007**, 9, 4183.



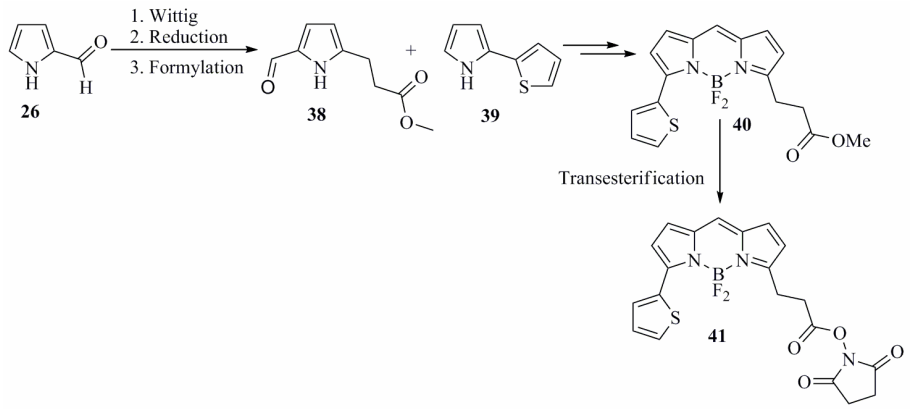
Scheme 11. Unexpected redox behaviour of intermediate nitrosopyrroles in the aza-dipyrrin condensation

1.2. Reactive BODIPY dyes

1.2.1. Synthesis of functionalized pyrrole building blocks

The most straightforward way of preparing functional BODIPY dyes is the introduction of the desired functional groups on the starting pyrrole building blocks. This approach has been explored extensively by Haugland, while looking for dyes that could be easily used as probes in biological research.[20] Although the required synthesis route can be lengthy and low yielding, it does allow for the introduction of a large variety of functional groups and substituents.

Examples of this approach are the synthesis of red shifted dyes **41** and **45** for conjugation to proteins.[20] Standard chemistry starting from pyrrole aldehyde **26** allows the correct placement of a carboxylic ester **38**. Condensing the resulting aldehyde with 2-thienylpyrrole **39** followed by complexation leads to ester BODIPY **40** (Scheme 12). Transesterification with *N*-hydroxysuccinimide furnishes an activated ester **41**, with excellent reactivity towards amines.

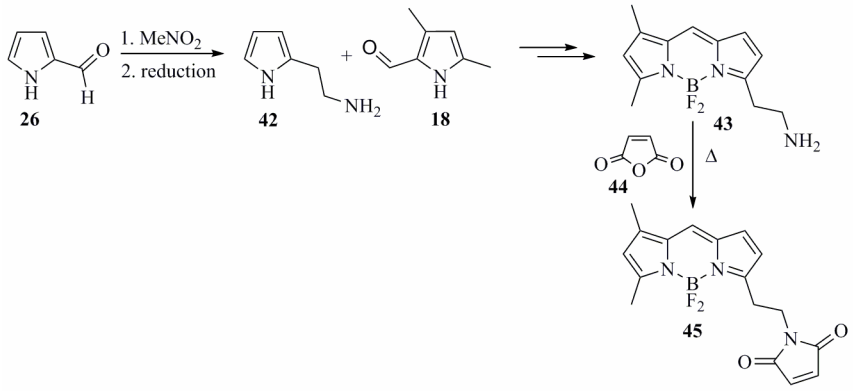


Scheme 12. The use of functionalized pyrroles for the synthesis of an amine labeling agent

In this manner, the synthesis of 2-aminoethylpyrrole **42** and the subsequent preparation of the BODIPY fluorophore results in an amine terminated BODIPY **43** (Scheme 13).[20] This amine can be condensed with maleic

20 (a) R. Haughland, H. Kang, **1988**, US Patent US4774339; (b) F. Monsma, A. Barton, H. Kang, D. Brassard, R. Haughland, D. Sibley, *J. Neurochem*., **1989**, 52, 1641; (c) H. Kang, H. Haughland, **1993**, US Patent 5187288.

anhydride **44** to form a maleimide **45**. Such maleimides can be functionalized highly selectively with sulfur nucleophiles, like cysteine residues in proteins, in a Michael type addition.



Scheme 13. The use of functionalized pyrroles for a cysteine labeling agent

Despite the obvious flexibility of this method, the laborious pyrrole synthesis is a drawback. Also, most of these systems that could be accessed with minimal synthetic effort are currently covered by patents of Molecular Probes (Invitrogen).[20]

1.2.2. Functionalisation *via* the *meso* substituent

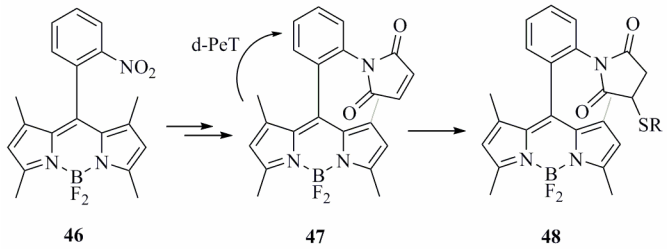
As the synthesis of dipyrrin ligands is a field well known from porphyrin chemistry, the methods described there have also been used for the preparation of BODIPY dyes. As mentioned previously, the condensation of an aromatic aldehyde with pyrroles, followed by oxidation and complexation leads to the desired fluorophores.[21] The main advantages of this synthetic pathway are the availability of aromatic aldehydes, the possibility for post-synthetic modification and the lack of direct effects on the spectroscopic properties upon changing the *meso* group.

This led to abundant use of the *meso* aryl group as a synthetic handle for the introduction of functional groups.[22] For example, *via* a standard synthetic route starting from 2-nitrobenzaldehyde and dimethylpyrrole **1**, one is able to

21 (a) R. Wagner, J. Lindsey, *J. Am. Chem. Soc*., **1994**, 116, 9759; (b) C. Bruckner, V. Karunaratne, S. Rettig, D. Dolphin, *Can. J. Chem*., **1996**, 74, 2182.

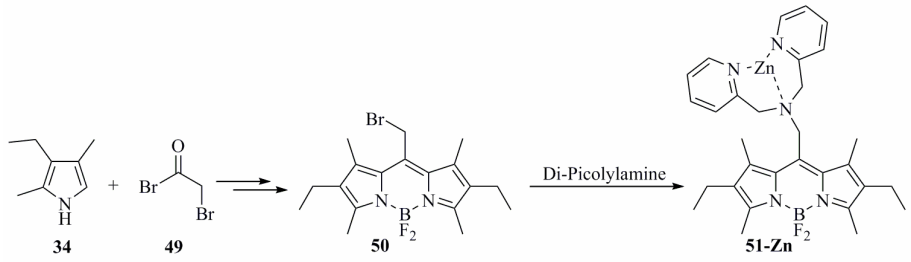
22 (a) H. Kim, J. Kim, *Tetrahedron Lett.*, **2006**, 47, 7051; (b) Y. Mei, P. Bentley, W. Wang, *Tetrahedron Lett.*, **2006**, 47, 2447; (c) T. Werner, C. Huber, S. Heinl, M. Kollmannsberger, J. Daub, O. Wolfbeis, *Fresenius J. Anal. Chem*., **1997**, 359, 150.

obtain dye **46** (Scheme 14). The electron withdrawing nitro group leads to a strongly diminished quantum yield (d-PeT), but upon reduction to the amine, fluorescence is restored.[23] Again, condensation with maleic anhydride leads to a maleimide **47**, which is also non fluorescent. However, as this dye **48** reacts with thiol groups, the electron transfer is quenched, and OFF-ON sensing behaviour for sulfur nucleophiles is observed.



Scheme 14. Introduction of a *meso* substituent in the design of an OFF-ON sensor for thiols

A *meso* substituent is not always introduced though the above-mentioned condensation-oxidation sequence, but can also originate from an acylpyrrole equivalent. As such, when bromo acetylbromide **49** reacts with densely substituted kryptopyrrole **34**, BODIPY **50** with a pending bromomethyl group is formed (Scheme 15). These systems have been applied in several projects,[24] such as the synthesis of a fluorescent probe for zinc ions **51**.[25] In the absence of the metal, the electron lone pair of the amine is donated to the electron poor BODIPY system (acceptor or reductive PeT), rendering it non fluorescent. Upon complexation of metal ions, the a-PeT is shut down, and fluorescence is restored.



Scheme 15. Substitution of a pending bromomethyl group in the synthesis of a sensor for zinc ions

23 T. Matsumoto, Y. Urano, T. Shoda, H. Kojima, T. Nagano, *Org. Lett.*, **2007**, 9, 3375.

24 (a) F. Amat-Guerri, M. Liras, M. Carrascoso, R. Sastre, *Photochem. Photobiol.*, **2003**, 77, 577; (b) N. DiCesare, J. Lakowicz, *Tetrahedron Lett*., **2001**, 42, 9105.

25 Y. Wu, X. Peng, B. Guo, J. Fan, Z. Zhang, J. Wang, A. Cui, Y. Gao, *Org. Biomol. Chem*., **2005**, 3, 1387.

1.2.3. The use of reactive methyl substituents

Just like in pyridine systems,[26] the 3,5-methyl groups on a BODIPY dye **52** are relatively acidic. This acidity allows the fluorophores to be condensed with aromatic aldehydes to form double bonds in a Knoevenagel type reaction (Scheme 16).[27] These reactions normally take place under basic conditions or in buffer, and require the removal of water from the mixture. This can be done by azeotropic removal of the water by a Dean-Stark apparatus, or by using molecular sieves. Although the ease of these reactions has led to widespread use, yields are often low or not reported in literature. Also, several electron poor aldehydes have been found unreactive under these conditions.

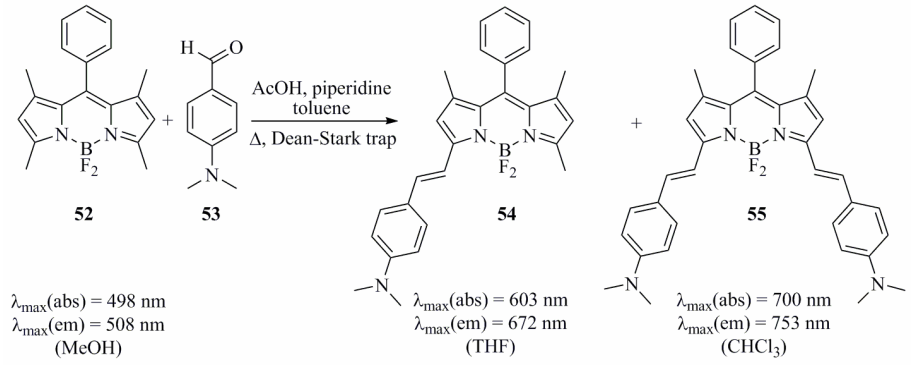
The use of electron donating substituents on the aromatic aldehyde **53** shifts the absorbance and fluorescence spectra even further to the red, and some of the BODIPY dyes prepared in this manner emit deep in the Near Infrared (NIR). The placement of electron donating substituents at the *para* positions leads to an additional red shift,[28] and the most striking red shift is observed with *p*-dimethylaminostyryl substituents **54** and **55**.[29] The conjugation of the nitrogen lone pair into the systems results in NIR emitting dyes that respond to protonation with a hypsochromic shift.

26 S. Shimizu, N. Watanabe, T. Kataoka, T. Shoji, N. Abe, S. Morishita, H. Ichimura, *Ullmann's Encyclopedia of Industrial Chemistry, Pyridine and Pyridine Derivatives*, Wiley, **2002**.

27 (a) K. Rurack, M. Kollmannsberger, J. Daub, *New J. Chem.*, **2001**, 25, 289; (b) A. Coskun, E. Akkaya, *Tetrahedron Lett*., **2004**, 45, 4947.

28 Z. Dost, S. Atilgan, E. Akkaya, *Tetrahedron*, **2006**, 62, 8484.

29 (a) Y. Yu, A. Descalzo, Z. Shen, H. Rohr, Q. Liu, Y. Wang, M. Spieles, Y. Li, K. Rurack, X. You, *Chem. Asian J*., **2006**, 1, 176; (b) M. Baruah, W. Qin, C. Flors, J. Hofkens, R. Vallee, D. Beljonne, M. Van, der Auweraer, W. De Borggraeve, N. Boens, *J. Phys. Chem. A*, **2006**, 110, 5998; (c) K. Rurack, M. Kollmannsberger, J. Daub, *Angew. Chem., Int. Ed*., **2001**, 40, 385.



Scheme 16. Condensation of 3,5-methyl substituents with aromatic aldehydes to yield alkenyl systems

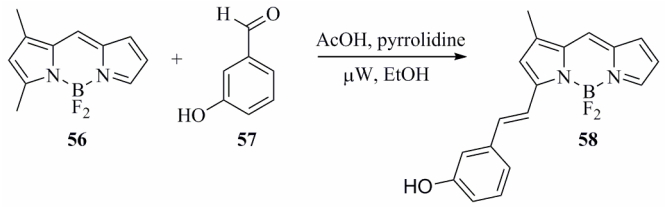
Many sensors have been prepared using these protocols, including those for transition metals,[30] pH,[31] and anions.[32] A particular example is the use of a library of aromatic aldehydes in the microwave mediated condensation with 1,3-dimethyl-BODIPY **56** (Scheme 17).[33] The reaction mixtures were purified by HPLC, and screened for selectivity towards glucagon. From this library of styrylated BODIPY dyes, compound **58** emerged as the only compound showing selectivity for glucagon, with an increase of fluorescence. The compound retained this selectivity in the presence of 16 other analytes, such as insulin and cytochrome c, and is a first example of BODIPY-library based screening for sensors rather than rational design. It also shows one of the techniques used as a countermeasure against the generally low yields of the condensation reaction, being microwave heating.

30 X. Qi, E. Jun, L. Xu, S. Kim, J. Hong, Y. Yoon. J. Yoon, *J. Org. Chem*., **2006**, 71, 2881.

31 J. Rostron, G. Ulrich, P. Retailleau, A. Harriman, R. Ziessel, *New J. Chem.*, **2005**, 29, 1241.

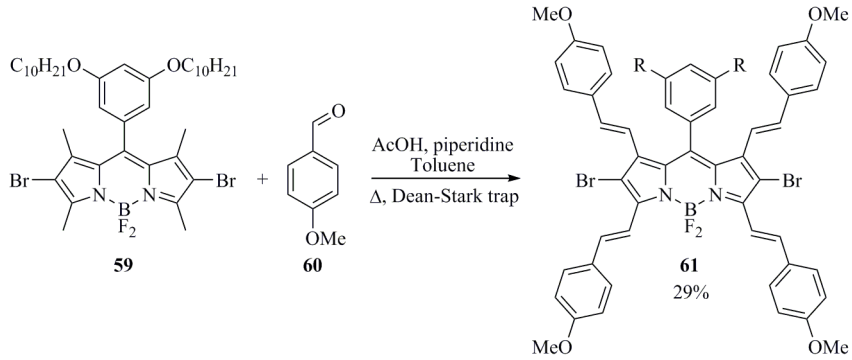
32 (a) Z. Ekmekci, M. Yilmaz, E. Akkaya, *Org. Lett*., **2008**, 10, 461; (b) A. Coskun, E. Deniz, E. Akkaya, *Tetrahedron Lett*., **2007**, 48, 5349.

33 L. Jun-Seok, K. Nam-Young, K. Yun Kyung, S. Animesh, F. Suihan, K. Hyeong, H. Vendrell, M.; Park, J. Hwan, C. Young-Tae, *J. Am. Chem. Soc.*, **2009**, 131, 10077.



Scheme 17. The use of α-methyl condensation reactions for the synthesis of a sensor for glucagons

Recently, Akkaya et al. used forcing conditions to get also the 1,7-methyl groups of BODIPY **59** to react, and form tetrastyryl dyes **61**.[34] In order to get this reaction running, they had to increase the acidity by the introduction of bromine atoms at the 2,6-positions (Scheme 18).

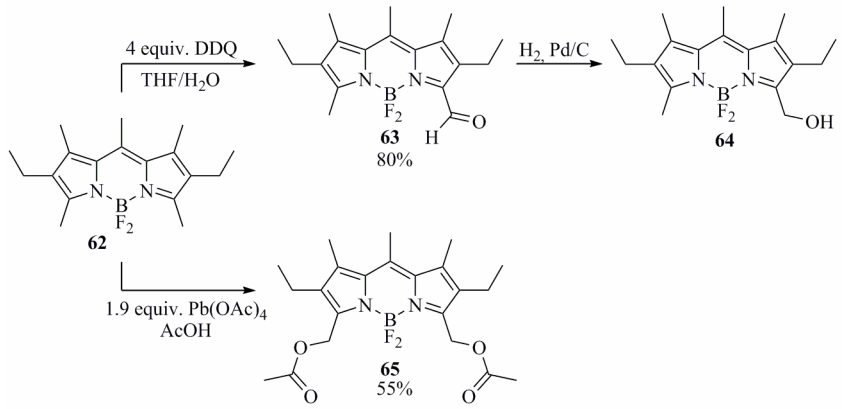


Scheme 18. Bromines enhance the acidity of the methyl substituents and allow quadruple condensation

These 3,5-*pseudo*-benzylic positions are also readily oxidized (Scheme 19). Thus, upon stirring the heavily substituted dye **62** with 4 equivalents of DDQ in aqueous THF, a single methyl group was oxidized to the corresponding aldehyde **63** in high yield, and this aldehyde could be reduced to the alcohol **64**.[35] Such compounds would be difficult to reach *via* standard pyrrole chemistry. Similarly, a change of oxidizer from DDQ to lead tetraacetate results in the double ester **65**.[35] Other groups than methyl can be oxidized and the use of such reactions on cyclohexane fused analogs led to the cyclohexanone.[35]

34 O. Buyukcakir, O. Bozdemir, K. Altan, S. Kolemen, S. Erbas, E. Akkaya, *Org. Let.*, **2009**, 11, 4644.

35 (a) T. Chen, J. Boyer, M. Trudell, *Heteroat. Chem.*, **1997**, 8, 51; (b) G. Sathyamoorthi, L. Wolford, A. Haag, J. Boyer, *Heteroat. Chem.*, **1994**, 5, 245.



Scheme 19. Oxidation of the 3,5-methyl substituents

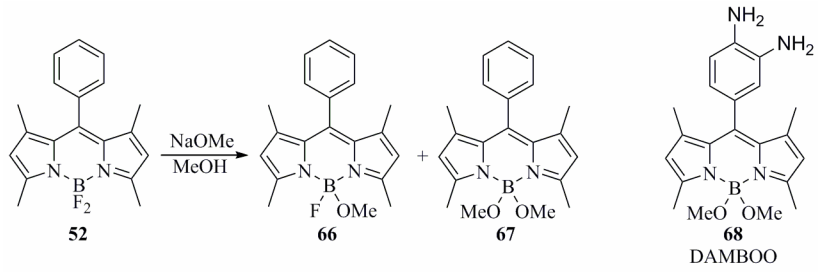
1.2.4. Substitution on the boron centre

Several papers have been dedicated to the substition of the fluorine atom on the boron centre. As the boron atom forms a hard centre, it can be readily substituted with hard nucleophiles.

Oxygen nucleophiles expel the fluorine atoms both under basic and Lewis acidic conditions. Thus, refluxing dye **52** in basic methanol led to a mixture of monosubstituted **66** and disubstituted product **67** (Scheme 20).[36] There is very little effect of the replacement of fluoride by methoxide, but it was noted that introduction of methoxide substituents increased the water solubility of the dyes. Furthermore, the new methoxy substituents did change the redox behaviour of the dye. This was used by Nagano et al. to optimize the electron transfer characteristics of their nitrous oxide sensor, to DAMBOO **68**.[37]

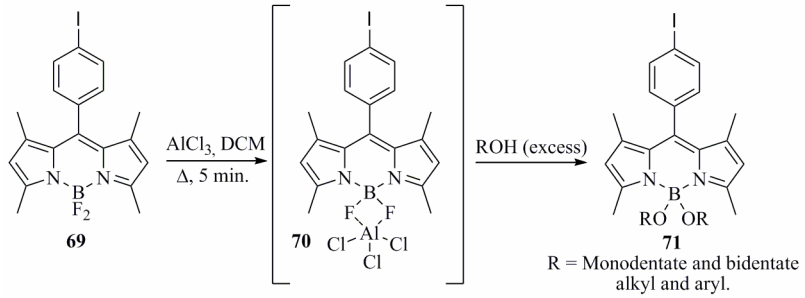
36 Y. Gabe, T. Uneo, Y. Urano, H. Kojima, T. Nagano, *Anal. Bioanal. Chem.*, **2006**, 386, 621.

37 (a) X. Zhang, H. Wang, J. Li, H. Zhang, *Anal. Chim. Acta*, **2003**, 481, 101; (b) Y. Gabe, Y. Urano, K. Kikuchi, H. Kojima, T. Nagano*, J. Am. Chem. Soc*., **2004**, 126, 3357.



Scheme 20. Alkoxide substitution of fluoride atom on the boron centre and the application in an improved NO sensor DAMBOO

Stirring BODIPY dyes **69** in dichloromethane with aluminium trichloride presumably activates the fluorine atoms via an intermediate **70**, as can be observed by the rapid disappearance of the starting material.[38] Addition of an excess of alcohol at this stage leads to efficient substitution of the fluorine by the alcohol (Scheme 21). The spectral properties of these alkoxylated dyes **71** are not clear, as in some cases no definite effect is observed, and in other cases, the fluorescence is totally quenched. However, the photostability of the resulting dyes is notably lower than in the case of difluorinated fluorophores.



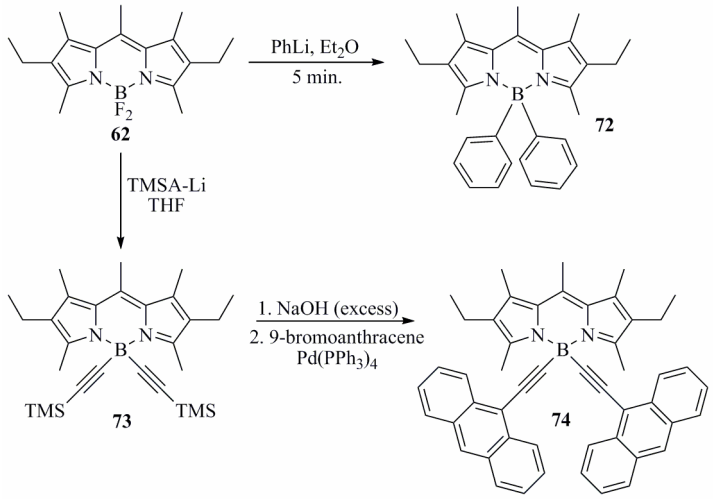
Scheme 21. Aluminium trichloride mediated fluoride substitution by alcohols

Carbon nucleophiles can also attack at the boron centre, and the group of Ziessel has made extensive use of this strategy. Both alkynyl and aryl anions, in the form of Grignard and organolithium reagents, readily substitute the fluorine atoms (Scheme 20).[39] A particular application of these reactions is combination of another chromophore with the BODIPY dye. Through space

38 C. Tahtaoui, C. Thomas, F. Rohmer, P. Klotz, G.. Duportail, Y. Mely, D. Bonnet, M. Hibert, *J. Org. Chem.*, **2007**, 72, 269.

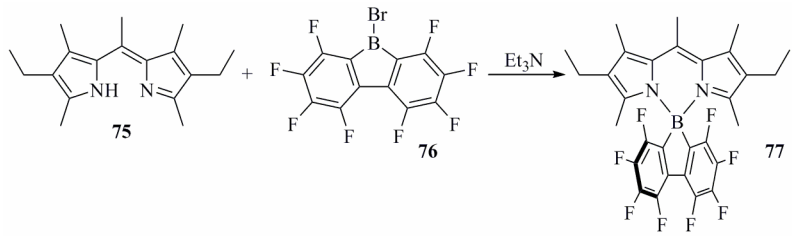
39 (a) G. Ulrich, C. Goze, M. Guardigli, A. Roda, R. Ziessel, *Angew. Chem., Int. Ed.*, **2005**, 117, 3760; (b) C. Goze, G. Ulrich, L. Mallon, B. Allen, A. Harriman, R. Ziessel, *J. Am. Chem. Soc*., **2006**, 128, 10231; (c) A. Harriman, G. Izzet, R. Ziessel, *J. Am. Chem. Soc*., **2006**, 128, 10868.

energy transfer from the donor dye to an acceptor BODIPY results in dye systems **74** with an artificially enhanced Stokes shift. Using similar reactions, also water solubilizing groups have been introduced.[40]



Scheme 22. Some examples of fluorine substitution by organometallic nucleophiles

Applying a boron source other than boron trifluoride in the complexation of the dipyrrin **75**, immediately results in a boron substituted dye (Scheme 23). However, presumably due to the high toxicity and limited stability of trivalent boron reagents, the use of these reagents in the complexation step is not widespread.[41] Nonetheless, using this approach, Thompson and co-workers recently prepared several BODIPY dyes **77** with perfluorinated substituents on the boron centre.[42]



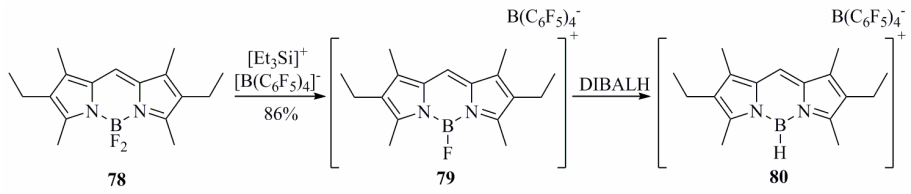
Scheme 23. The use of functionalized boron reagents in the complexation with dipyrrins

40 P. Didier, G. Ulrich, Y. Mely, R. Ziessel, *Org. Biomol. Chem*., **2009**, 7, 3639.

41 H. Kee, C. Kirmaier, L. Yu, P. Thamyongkit, W. Youngblood, M. Calder, L. Ramos, B. Noll, D. Bocian, W. Scheidt, R. Birge, J. Lindsey, D. Holten, *J. Phys. Chem. B*, **2005**, 109, 20433.

42 C. Bonnier, W. Piers, A. Al-Sheikh, A. Thompson, M. Parvez, *Organometallics*, **2009**, 28, 4845.

Recent work by Bonnier and co-workers has focused on the use of defluorinated BODIPY as the synthon for fluoride substitution on the boron.[43] Halide abstraction of a heavily substituted BODIPY **78** results in the precipitation of a cationic boron derivative **79** (Scheme 24). This purple dye is stable in solid form, but decomposes slowly in solution. Displacement of the remaining fluoride with DIBALH as hydride source rapidly led to a deep blue borenium hydride **80**. Such systems are currently studied for the preparation of asymmetric BODIPY systems.



Scheme 24. Reductive synthesis of BODIPY-borenium cations

1.2.5. Halogenated BODIPY dyes

Considerable effort has been placed in the synthesis of halogenated BODIPY dyes, as these could be subjected to the plethora of reactions available for halogenated aromatic heterocycles. Among the synthetic strategies available, one can distinguish between halogenation after the complexation and halogenation at some pyrrolic stage. So far, halogenation at the dipyrrin stage has only been reported for aza-BODIPY dyes.[16]

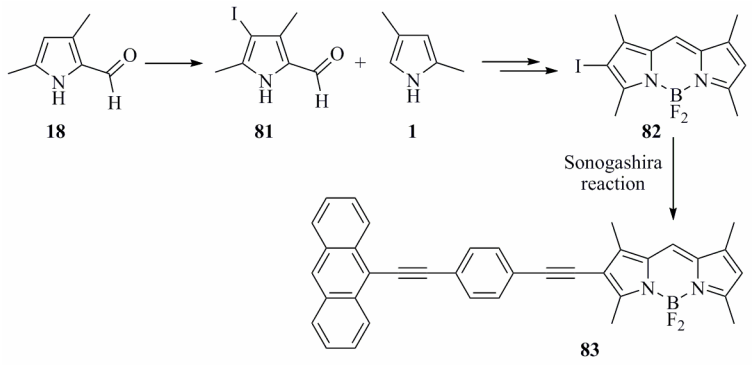
1.2.5.1. From halogenated pyrroles

The higher electron density of pyrrolic precursors makes them susceptible to electrophilic halogenation, and careful selection of the pyrrolic building blocks can result in dyes with proper functionalities. Reports of this approach are few, but the systems have been used in palladium catalyzed coupling reactions.[44] Iodination of 3,5-dimethyl-2-pyrrolecarboxaldehyde **18** and condensing product **81** with dimethylpyrrole **1** to monoiodinated BODIPY **82** provides an excellent scaffold for elaboration with Sonogashira coupling (Scheme 25). Anthracene substituted dye **83** is an example thereof, and undergoes rapid energy transfer from the anthracene to the boron

43 C. Bonnier, W. Piers, M. Parvez, T. Sorensen, *Chem. Commun*., **2008**, 38, 4593.

44 (a) T. Kim, J. Castro, A. Loudet, J. Jiao, R. Hochstrasser, K. Burgess, M. Topp, *J. Phys. Chem*., **2006**, 110, 20; (b) C. Wan, A. Burghart, J. Chen, F. Bergström, L. Johansson, M. Wolford, T. Kim, M. Topp, R. Hochstrasser, K. Burgess, *Chem. Eur. J.*, **2003**, 9, 4430.

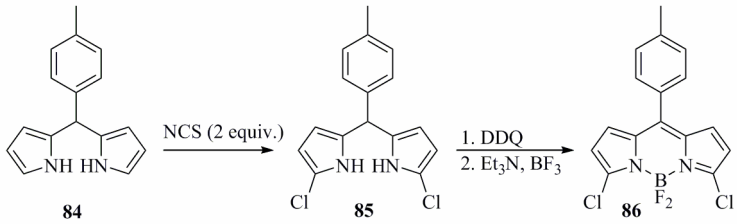
fluorophore. In fact, this transfer is too fast to be measured, which has been attributed to the beneficial alignment of transition moments.



Scheme 25. Halogenation of a pyrrole followed by incorporation in a BODIPY fluorophore, and the use of this halogenated dye in a Sonogashira reaction

1.2.5.2. 3,5-Dihalogenated BODIPY dyes

However, it is also possible to halogenate after the initial condensation of pyrrole with an aromatic aldehyde (Scheme 26). Dipyrromethane **84** is still highly reactive towards halogenation, but blocking the reactive α-positions leads to increased stability.[45] The intermediate dichlorinated dipyrromethane **85** can be isolated by column chromatography, but a more convenient immediate oxidation and complexation results in a 3,5-dichlorinated BODIPY dye **86**.[46] Recently, substituting N-chlorosuccinimide (NCS) with N-bromosuccinimide (NBS) has led to the synthesis of the dibromo analogue.[47]



Scheme 26. Dichlorination at the dipyrromethane stage, followed by oxidation and complexation

These 3,5-dihalogenated systems, introduced by Dehaen and Boens, can be readily substituted with a wide range of nucleophiles.[48] Conducting the reaction at room temperature leads to a monosubstituted product, while reaction at elevated temperatures with an excess of nucleophile results in the disubstituted product (Scheme 27). Using these procedures, sulfur (**87b)**, oxygen (**87a** and **88a)**, nitrogen (**87c** and **88c)** and carbon (**87g** and **88g)** substituted products could be obtained in moderate to excellent yields. The introduction of these groups strongly influences the spectroscopic properties of the resulting products (Table 1). Substitution with amines and thiols shifts the absorption and emission bands to the red, substitution with oxygen nucleophiles and malonate groups has no distinct effect. Recently, some more exotic examples have been reported, in a study of selenium and tellurium functionalized dyes (**88d-f**).[48]

45 J. Strachan, D. O'Shea, T. Balasubramanian, J. Lindsey, *J. Org. Chem*., **2000**, 65, 3160.

46 (a) M. Baruah, W. Qin, R. Vallee, D. Beljonne, T. Rohand, W. Dehaen, N. Boens, *Org. Lett*., **2005,** 7, 4377; (b) T. Rohand, M. Baruah, W. Qin, N. Boens, W. Dehaen, *Chem. Commun*., **2006**, 266.

47 S. Rihn, P. Retailleau, N. Bugsaliewicsz, A. De Nicola, R. Ziessel, *Tetrahedron Lett*., **2009**, 50, 7008.

48 E. Fron, E. Coutino-Gonzalez, L. Pandey, M. Sliwa, M. Van der Auweraer, F. De Schryver, J. Thomas, Z. Dong, V. Leen, M. Smet, W. Dehaen, T. Vosch, *New J. Chem.*, **2009**, 33, 1490.

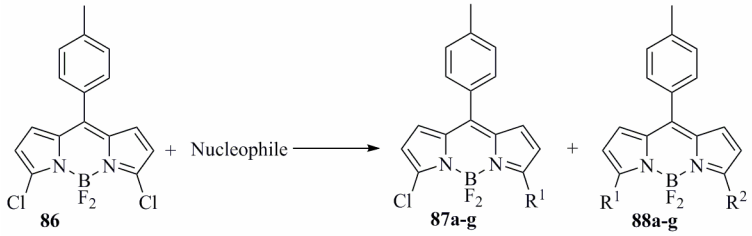


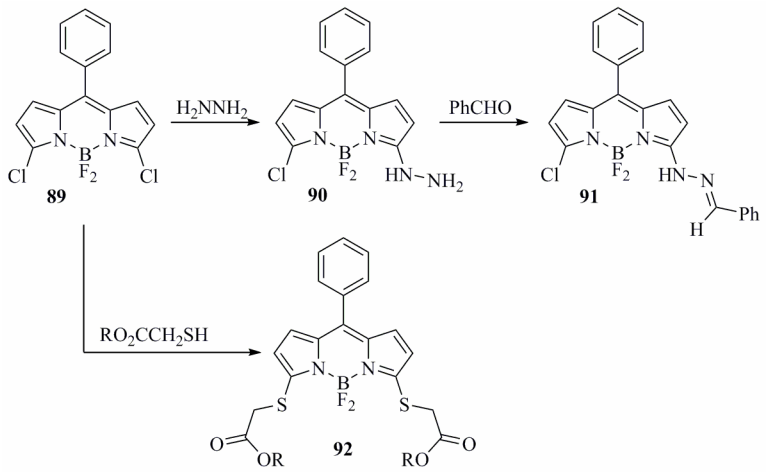
Table 1: Nucleophilic substitution of 3,5-dichlorinated BODIPY dyes and the effect thereof on the spectroscopic properties.

Product	R^1	R^2	λ_{max}(abs)	λ_{max}(em)	ϕ_{fl}
86[a]	Cl	Cl	516	529	0.63
87a[a]	OMe	-	508	520	0.08
88a[a]	OMe	OMe	513	525	0.13
88b[b]	SPh	SPh	582	602	0.84
87c[a]	NHPh	-	524	575	0.35
88c[a]	NHPh	NHPh	597	623	0.61
88d[b]	SePh	OMe	552	574	0.76
88e[b]	SePh	SePh	591	612	0.72
88f[b]	TePh	TePh	626	658	0.03
88g[a]	$(EtO_2C)_2CH$	-	514	526	0.46
88g[a]	$(EtO_2C)_2CH$	$(EtO_2C)_2CH$	515	527	0.62

a) Data in toluene b) data in cyclohexane

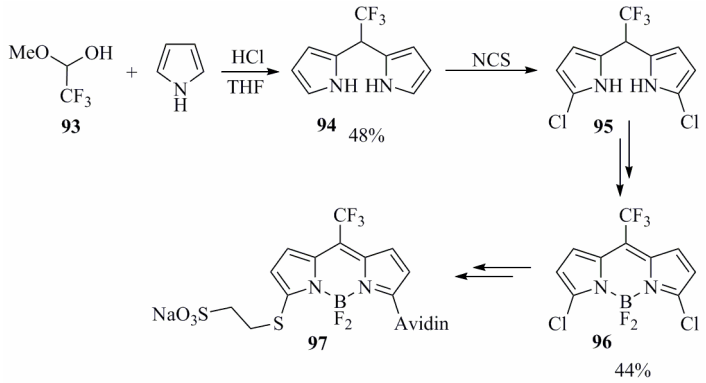
Dilek and Bane substituted the 3,5-dichloro dye **89** with hydrazine, and reacted the resulting product **90** with carbonyl compounds to form hydrazones **91** (Scheme 27).[49] Hydrazone formation has been used as an orthogonal method for the labeling of proteins. Interestingly, hydrazones formed from either aliphatic or aromatic aldehydes could be distinguished spectroscopically. More recently, the same group substituted similar dyes with thioacetic acid **92**, thus introducing water solubility and a handle for protein labelling.[50]

49 O. Dilek, S. Bane, *Tetrahedron Lett.*, **2008**, 49, 1413.
50 O. Dilek, S. Bane, *Bioorg Med Chem Lett.*, **2009**, 19, 6911.



Scheme 27. 3,5-Dichloro-BODIPY in the synthesis of protein labels

This approach has been followed by several other groups. Burgess et al. prepared similar, dichlorinated systems **96** with a *meso*-trifluoromethyl group (Scheme 28).[51] The electron withdrawing nature of this group renders the system more reactive to nucleophiles, while it has strongly enhanced quantum yields. These compounds were reacted with avidine to **97** and the loading was studied spectroscopically.

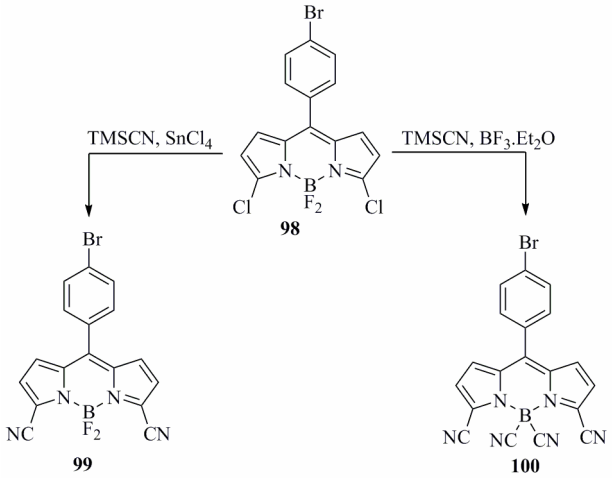


Scheme 28. Synthesis and substitution of a meso-trifluoromethyl-3,5-dichloro-BODIPY

During the same study, Burgess and co-workers also looked deeper into the differences between hard and soft nucleophiles. As mentioned before, hard nucleophiles tend to attack the boron centre, and it appeared that soft nucleophiles preferentially substituted the 3,5-chlorine atoms. Borderline

51 L. Li, B. Nguyen, K. Burgess, *Bioorg. Med. Chem. Let.*, **2008**, 18, 3112.

nucleophiles, such as cyanide, also preferred the 3,5-positions yielding **99**, although this depends on the catalyst used (Scheme 29). Boron trifluoride as Lewis acid did allow for the boron cyanated products **100** to be isolated and studied spectroscopically.[52]



Scheme 29. Lewis acid activation dependency of the substitution behaviour of cyanide

Furthermore, these reactive chlorinated systems could be subjected to several transition metal catalyzed coupling reactions (Scheme 30), such as Suzuki and Stille arylation (**101a** and **102a)**, Sonogashira alkynylation (**101c** and **102c)** and Heck coupling with styrene (**101b** and **102b)**.[53] Again, in most of these cases, both the mono and disubstituted products could be obtained in variable yields. The Heck reactions can result in the formation of distyrylated dyes, analogous to the condensation reaction products **56**. Although these reactions can be carried out in reasonable to good yields, purification of the resulting mixtures to a degree of spectroscopic purity is often hard. The elongated conjugation leads to a pronounced red-shift as well as an increased quantum yield in all cases (Table 2). In particular, phenylethynyl substituents turn out to be highly interesting, combining a large red shift with an excellent quantum yield.

52 K. Cieslik-Boczula, K. Burgess, B. Nguyen, L. Pandey, W. De Borggraeve, M. Van der Auweraer, N. Boens, *Photochem. Photobiol. Sci*., **2009**, 8, 1006.
53 T. Rohand, W. Qin, N. Boens, W. Dehaen, *Eur. J. Org. Chem.*, **2006**, 4658.

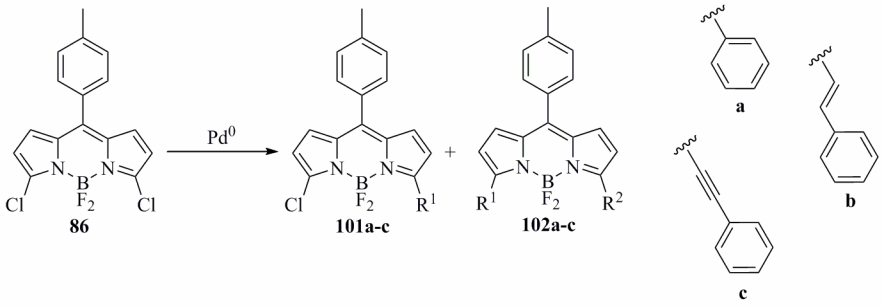


Table 2. Palladium catalyzed functionalisation of 3,5-dichlorinated BODIPY dyes, and the effect thereof on the spectroscopic properties

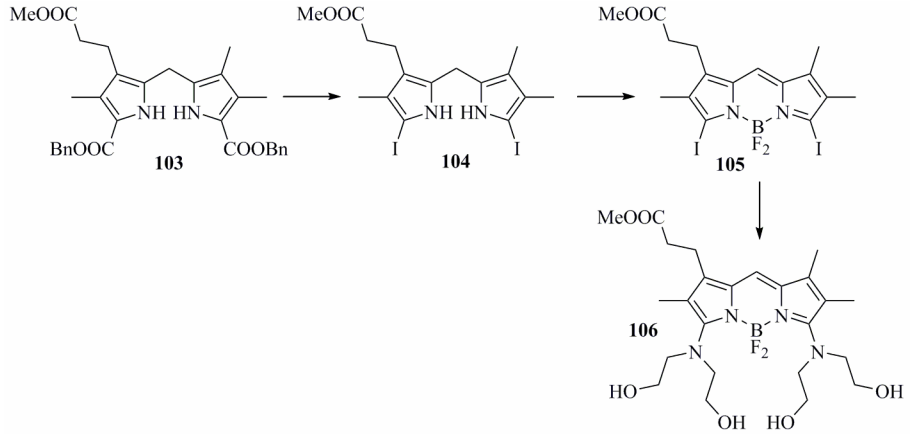
Product[a]	R^1	R^2	λ_{max}(abs)	λ_{max}(em)	ϕ_{fl}
101a	Ph	Cl	537	558	0.13
102a	Ph	Ph	557	589	0.42
101b	CH=CHPh	Cl	572	588	0.69
102b	CH=CHPh	CH=CHPh	637	649	0.93
101c	C≡CPh	Cl	566	577	0.91
102c	C≡CPh	C≡CPh	614	629	1.00

a) all data in toluene

3,5-Diiodinated dyes **105** have also been reported, although they are prepared using a totally different approach (Scheme 30).[54] A saponification followed by halogenative decarboxylation, which is a well known procedure in pyrrole chemistry,[55] leads to diiodinated dipyrromethane **104**. Oxidation and complexation results in the 3,5-diiodinated fluorophore **105**, and this is still reactive towards nucleophiles, as was exemplified by the synthesis of sensor **106** for Cu(II) in living cells.

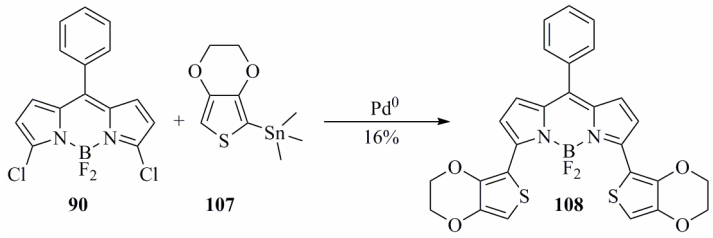
54 L. Jiao, J. Li, S. Zhang, C. Wei, E. Hao, M. Vicente, *Org. Biomol. Chem.*, **2009**, 33, 1888.

55 K. Smith, O. Minnetian, *J. Org. Chem.*, **1985**, 50, 2073.



Scheme 30. Synthesis and functionalization of a 3,5-diiodo-BODIPY

Applications of these reactions are now slowly appearing in the open literature. For example, Stille coupling reaction with a thienyl stannane **107** results in fluorophore **108** (Scheme 31) that can be polymerized to form fluorescent polymers.[56]



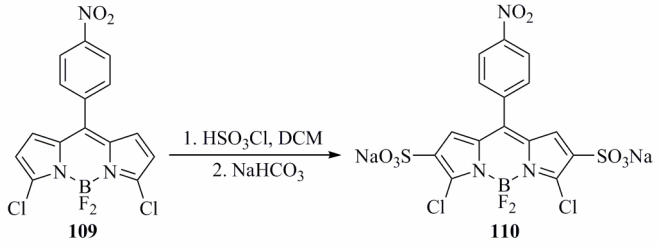
Scheme 31. Use of 3,5-dichlorinated BODIPY dyes for the preparation of thiophene BODIPY dyes towards conductive fluorescent polymers

These compounds were also sulfonated to induce water solubility, in a modified procedure of the initial work by Wories et al.[57] By adapting the experimental procedures, an optimized protocol was established (Scheme 32).[58] Chlorosulfonation is very fast at -78°C in dichloromethane, and after neutralization, the salt **110** can be isolated *via* column chromatography. The resulting dyes **110** are highly water soluble, and have a pending nitro substituent for the elaboration and labelling of biomolecules.

56 J. Forgie, P. Skabara, I. Stibor, F. Vilela, Z. Vobecka, *Chem. Mater.*, **2009**, 21, 1784.

57 H. Wories, J. Koek, G. Lodder, J. Lugtenburg, R. Fokkens, O. Driessen, G. Mohn, *Recl. Trav. Chim. Pays-Bas*, **1985**, 104, 288.

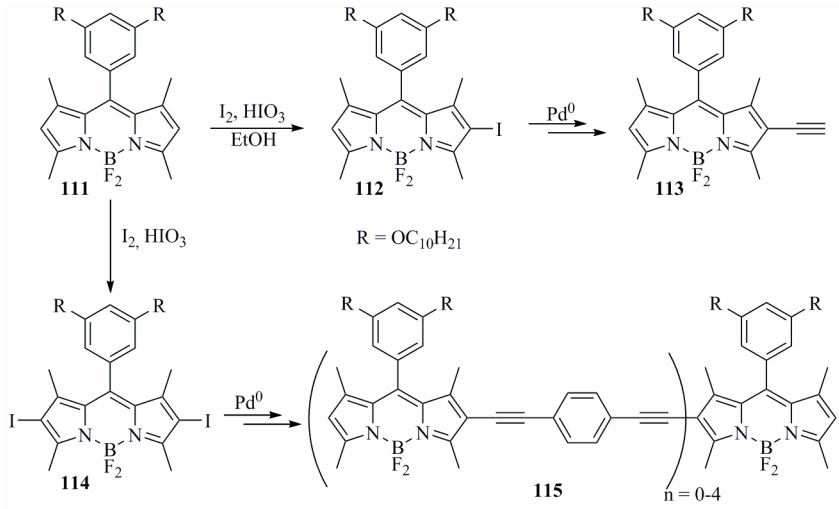
58 L. Li, J. Han, B. Nguyen, K. Burgess, *J. Org. Chem*., **2008**, 73, 1963.



Scheme 32. Synthesis of water soluble 3,5-dichlorinated systems

1.2.5.3. Halogenation after complexation

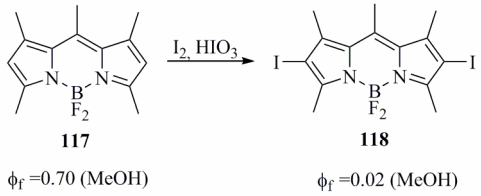
Perhaps the most widespread synthesis of halogenated BODIPY fluorophores relies on direct electrophilic halogenation. Selecting dyes with the desired substitution pattern is necessary, and both monosubstituted and disubstituted systems can be obtained. Lately, organometallic couplings on such halogenated systems have been used to incorporate BODIPY dyes in conjugated oligomers (Scheme 33).[59] Selective mono and diiodination (to dyes **112** and **114**, respectively) can be effected by changing the amount of iodine and the reaction times. These halogenations are followed by Sonogashira sequences, yielding several oligomers **115**. The extended conjugation leads to a large red-shift, although the cumulative effect decreases with increasing monomer units.



Scheme 33. Post condensation halogenation in the synthesis of conjugated fluorescent polymers

59 Y. Cakmak, E. Akkaya, *Org. Let.*, **2009**, 11, 85.

The introduction of iodine substituents strongly quenches the fluorescence, by favouring a spin forbidden transition to a triplet state. This triplet state could then be used to generate singlet oxygen. This highly toxic singlet oxygen can be used to target malignant cells, in photodynamic therapy (PDT). Thus, double iodination of **117** forms the non fluorescent dye **118** that has been shown to be a highly efficient sensitizer for PDT (Scheme 34).[60]

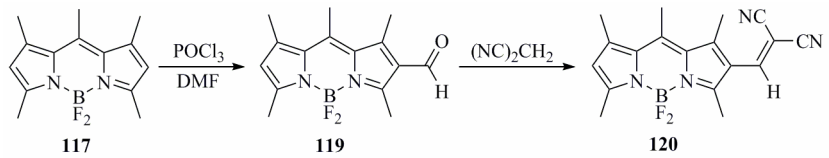


Scheme 34. 2,6-iodination as a means to shut down fluorescence and induce triplet state formation

1.2.6. Direct functionalization of the BODIPY core

Besides the previously mentioned halogenation and sulfonation of BODIPY dyes, direct substitution of the boron dipyrromethene dyes has been used for the introduction of several other functional groups. Such electrophilic substitutions on unsubstituted dyes suffer from regiochemistry issues, with mixtures of substitution at the 2,6-positions and 3,5-positions being formed. This is normally solved by the use of dimethylpyrrole for the preparation of the BODIPY dye, forcing the substituent to the 2,6-position.

In this fashion, the dye has been successfully subjected to nitration[61] and Vilsmeier formylation. The formylated dyes **119** were first mentioned by Burgess,[2] but published in full by Jiao who used these dyes in Knoevenagel condensations to afford **120** (Scheme 35).[62]

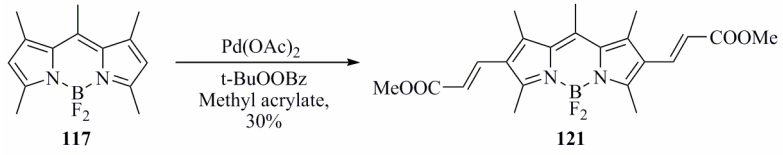


Scheme 35. Vilsmeier formylation followed by condensation with malonitrile

60 T. Yogo, Y. Urano, Y. Ishitsuka, F. Maniwa, T. Nagano, *J. Am. Chem. Soc*., **2005**, 127, 12162.
61 K. Takuma, T. Misawa, K. Sugimoto, T. Nishimoto, H. Tsukahara, T. Tsuda, G. Imai, H. Kogure, **1998**, JP Patent 10273504.
62 L. Jiao, C. Yu, J. Li, Z. Wang, M. Wu, E. Hao, *J. Org. Chem*., **2009**, 74, 7525.

Recently, a lot of attention has gone to the direct, transition metal catalyzed C-H functionalization.[63] Similar protocols can be applied to selected BODIPY dyes, although research into this subject is still limited.

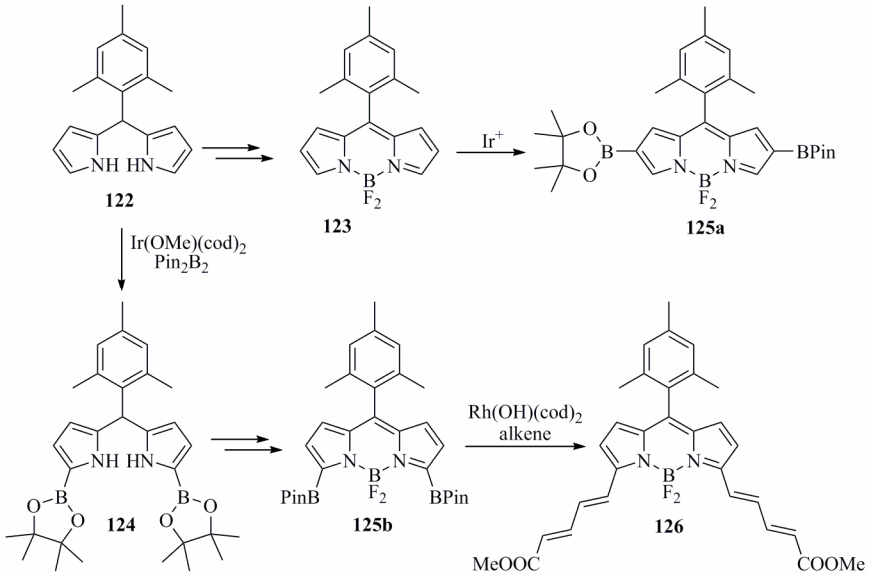
Illustrative is the palladium catalyzed addition of double bonds at the 2,6-positions, by Burgess et al. (Scheme 36).[64] Oxidative formation of an organopalladium(II)-BODIPY followed by Heck type vinylation leads to **121** in moderate yields. As Pd(0) is eliminated from the reaction, a reoxidizer was required in order to be able to use palladium in catalytic amounts.



Scheme 36. Direct hydrogen substitution under oxidative palladium mediated hydrogen substitution

By making use of the contrasting electron density pattern in a dipyrromethane and its corresponding BODIPY (Scheme 37), the group of Osuka was able to effect selective iridium catalyzed borylation at both these stages.[65] Oxidation and complexation of the substituted dipyrromethane then leads to complementary functionalized dyes **125a** and **125b**. Rhodium catalyzed Heck reaction of these borylated BODIPY fluorophores opens routes to both possible regioisomers of **126**.

63 (a) M. Chen and C. White, *Science*, **2007**, 318, 783; (b) H. Davies, R. Beckwith, *Chem. Rev.*, **2003**, 103, 2861; and references cited therein.
64 C. Thivierge, R. Bandichhor, K. Burgess, *Org. Lett*., **2007**, 9, 2135.
65 J. Chen, M. Mizumura, H. Shinokubo, A. Osuka, *Chem. Eur. J*., **2009**, 15, 5942.

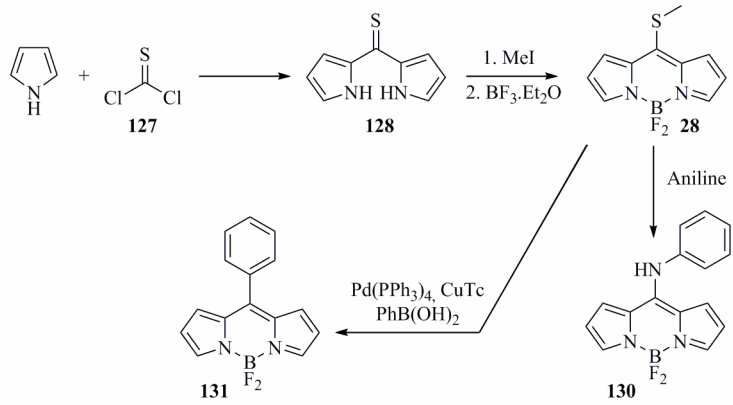


Scheme 37. Iridium catalyzed direct hydrogen substitution in combination with the complementary reactivity of dipyrromethanes and the boron dipyrrins

1.2.7. Thioether functionalized BODIPY fluorophores

Reaction of pyrrole with thiophosgene **127** rapidly generates thioketones **128**, that react with methyl iodide to produce thiomethylated dipyrrins (Scheme 38). After complexation, the highly fluorescent 8-thiomethyl BODIPY dyes **27** are obtained.[66] The *meso* position of dipyrrins has been known to be prone to substitution with nucleophiles, but normally reduction is observed. An addition-elimination mechanism with the thiomethyl substituent as leaving group takes place, and stirring thiomethylated dye **27** in the presence of aniline results in amine **130**.

66 T. Goud, A. Tutar, J. Biellmann, *Tetrahedron*, **2006**, 62, 5084.



Scheme 38. Synthesis and substitution of *meso*-thiomethylated BODIPY dyes

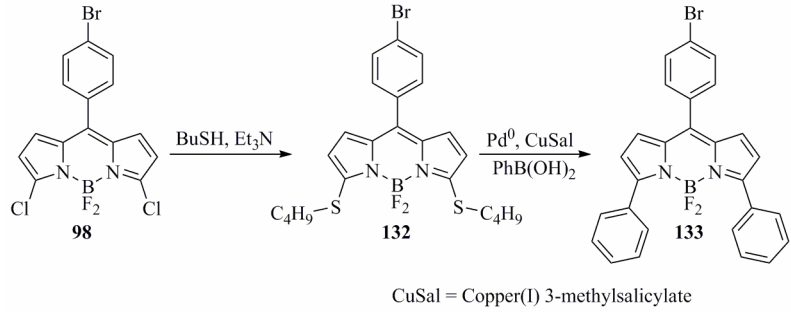
Peña-Cabrera et al. used this system in palladium catalyzed cross couplings.[67] Under palladium catalysis and with stochiometric amounts of copper salts, the thiomethyl group of **28** couples with boronic acids in excellent yields. This approach, an example of the Liebeskind-Srogl cross-coupling,[68] makes it possible to produce a large variety of *meso* substituted dyes from a single starting compound **28**. Generally, reactions are high yielding and fast, but they require an excess of boronic acid to reach completion.

In collaboration with Peña-Cabrera, the group of Burgess substituted the previously mentioned 3,5-dichloro BODIPY dyes **98** with butylthiol to yield the 3,5-bis-thioether **132** (Scheme 39).[69] These compounds were subsequently used in Liebeskind-Srogl reactions to **133**. Advantages of this method are the use of relatively mild and base free conditions, as well as the orthogonality with other palladium catalyzed cross couplings. Thus the bromine function of **133** remains untouched.

67 E. Peña-Cabrera, A. Aguilar-Aguilar, M. Gonzalez-Dominguez, E. Lager, R. Zamudio-Vazquez, J. Godoy-Vargas, F. Villanueva-Garcia, *Org. Lett*., **2007**, 9, 3985.

68 L. Liebeskind, J. Srogl*, J. Am. Chem. Soc.*, **2000**, 122, 11260.

69 J. Han, O. Gonzalez, A. Aguilar-Aguilar, E. Peña-Cabrera, K. Burgess, *Org. Biomol. Chem*., **2009**, 7, 34.



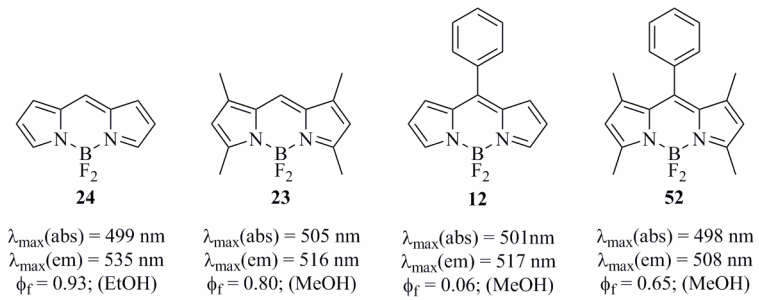
Scheme 39. The Liebeskind reaction is orthogonal to other cross couplings

1.3. Structural factors determine spectral properties

Combining the standard synthetic approaches towards the BODIPY system with the previously mentioned reactive systems has lead to an abundance of structures. The different substitution patterns result in a wide variety of spectral properties, and even though analysis thereof is not always straightforward, some general trends can be observed.

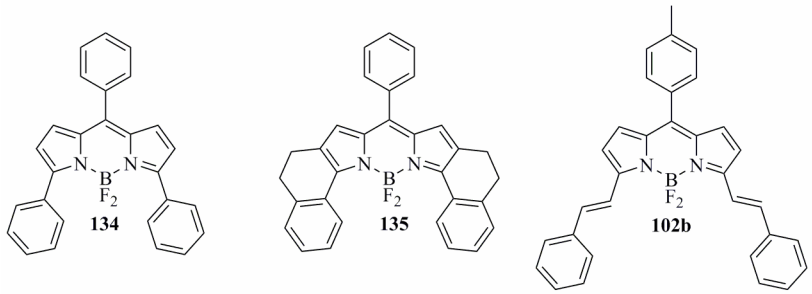
Substituting the dyes leads to an enhanced stability, both of the dye and its precursors. The introduction of alkyl groups, as in **23**, does not have a significant effect on the spectral properties. Just like the unsubsituted system **24** , they are highly fluorescent in both polar and apolar media.

Meso arylated dyes **12** generally have low quantum yields of fluorescence, and this has been attributed to fast rotation of the aryl group acting as a non radiative pathway of decay. Locking the rotation by placing methyl substituents at the 1,7 positions leads to an improved quantum yield of fluorescence for dye **52**. There is no conjugation between the aryl substituent and the fluorescent BODIPY core as both groups adopt a staggered structural arrangement to minimize sterical interactions.



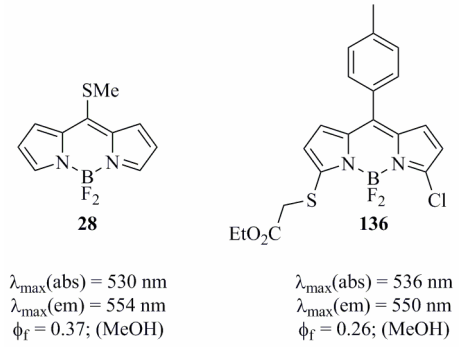
Scheme 40. Influence of alkyl and *meso* aryl substituents on the spectroscopic properties

The colour of the dye can be shifted to the red by increasing the conjugation. This is conveniently achieved by placing aryl groups on the system **134**. As the aryl groups are still free to rotate, the red shift is attenuated. On such systems, locking the rotation does not only lead to an increased quantum yield of fluorescence, but also a large bathochromic shift in **135**. Further extension of the conjugation with larger aromatic systems or alkenes to **102b** and alkynes **102c** shifts the absorption and emission maxima of the dyes even further to the red.



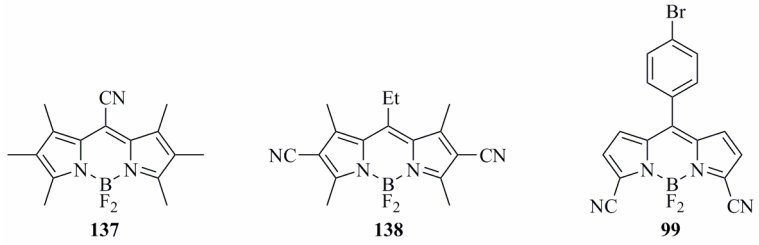
Scheme 41. The effect of extended conjugation, with and without restriction of the rotation.

Placing heteroatoms directly on the BODIPY core can have similar effects. The 8-thiomethylated dye **28** has red shifted absorption and emission maxima, and this is also true for a 3-sulfur substituted dye **136**. Again, lowering of the quantum yield due to rotation of the *meso* aryl is noted.



Scheme 42. Influence of electron donating nucleophiles placed directly on the dye

A peculiar effect is observed on *meso* cyanated dyes, which are strongly red shifted with retention of a high quantum yield. This shift is assigned to a lowering of the LUMO, reducing the energy gap for excitation. This effect seems to be limited to the 8-position, as both 2,6 and 3,5-cyano substituted dyes to not exhibit similar shifts.



Scheme 43. *Meso* cyano substituted dyes exhibit red shifted absorption and emission.

As such, knowledge of these structural traits can help identifying the target dye for a specific application. For example, the much sought after dyes that combine red shifted absorption and emission maxima with a high quantum yield of fluorescence most likely have extended conjugated systems, and lack rotating moieties.

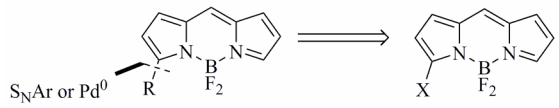
1.4. Conclusion

The BODIPY system has come a long way from its initial discovery, and is now well established as a versatile fluorophore. During the last decade, a wide range of synthetic approaches and structural variations has been reported in literature. However, with new and ingenious applications of these dyes soaring in the last years, there is still plenty of room for the development of novel and improved ways of modifying the system.

2. Goals and objectives

The main target of the research is an exploration of reactive BODIPY dyes. The design and synthesis of such fluorophores, which can be reached with minimal synthetic effort, but maximal functionalization potential, may facilitate the use of BODIPY dyes even further.

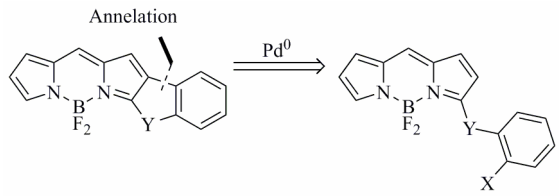
In a first part of the research, the synthesis of novel halogenated boron dipyrrin systems should lead to improved reactivity when compared to the 3,5-dichlorinated dyes that were described earlier. Mainly in transition metal catalyzed reactions there is room for improvement, alleviating the need for microwave heating in Suzuki coupling and obtain improved yields for the Sonogashira reaction.



Scheme 44. Design of 3-halogenated BODIPY dyes with reactivity in nucleophilic aromatic substitution and transition metal catalyzed reactions

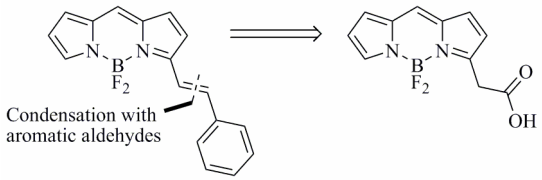
From such modular approach, the properties of the dyes should be tuneable, and a full control of both spectroscopic as physicochemical properties should be attainable. Synthetic control of the system could be even further improved by the preparation of multiply halogenated dyes or sulfur substituted compounds.

In a second part, a nucleophilic aromatic substitution followed by palladium catalyzed heterocycle fusion will be investigated as a new strategy towards red shifted BODIPY dyes. Such restricted systems are highly sought after, but remain a synthetic challenge with laborious pyrrole syntheses. Again, a modular approach would allow fast preparation of the dyes, with control of the resulting properties.



Scheme 45. Oxidative, transition metal catalyzed ring formation towards conformationally restricted dyes

Thirdly, as condensation reactions between aromatic aldehydes and the 3,5-methyl substituents of BODIPY dyes are currently used as one of the main approaches to functionalization, even though they suffer from low yields, an optimisation of the condensation procedures would be highly beneficial. A Doebner type condensation between BODIPY acetic acids and aromatic aldehydes will be designed. For this purpose, esters of acetic acid have to be introduced directly on the BODIPY core, and this could be done through traditional pyrrole chemistry or substitution reactions.



Scheme 46. BODIPY acetic acids as the starting point for condensation reactions with aromatic aldehydes

Finally, the reactive systems prepared in the first stages of the project will be used in proof of concept applications, showing the potential of our new compounds.

A main use of fluorescent dyes will be the preparation of sensors for a variety of substrates. Through nucleophilic substitutions on our BODIPY dyes, rapid preparation of novel sensors could be envisaged.

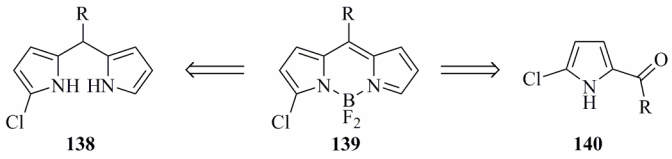
Fluorescent molecules are also often used in biomedical research. Several systems are designed that employ modern reactions to prepare protein-BODIPY conjugates. Similar methods would allow the introduction of these highly fluorescent compounds in novel materials such as conjugated polymers.

3. Results

3.1. Monohalogenated BODIPY dyes

3.1.1. One halogen instead of two

Drawbacks of the previously mentioned dichlorinated systems **86** are the need for disubstitution to avoid a remaining reactive position,[46] and problems occurring during some palladium catalyzed coupling reactions.[53] Notably in the Sonogashira reaction, the selectivity for monosubstitution is low and the resulting products are hard to isolate in pure form. Also, Suzuki reactions only proceed at an acceptable rate under microwave irradiation.[53] We are convinced that most of these problems can be solved by the synthesis of monohalogenated BODIPY dyes **139**.
However, expanding the previously reported methods to monohalogenation of the dipyrromethane (Scheme 47) precursors to **138** resulted only in complex reaction mixtures. The deactivation by the first halogen appears to be insufficient to ensure only one halogenation.
Since the acid catalyzed condensation of an acylpyrrole and a second pyrrole is a well known method for preparing dipyrromethenes,[5] the precursors of BODIPY, we reasoned that the synthesis of the desired products could be reduced to the preparation of 2-acyl-5-halopyrroles **140**.



Scheme 47. Retrosynthesis of monohalogenated BODIPY dyes

3.1.2. Synthesis

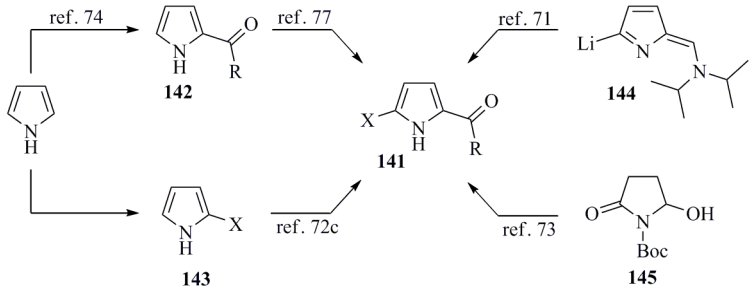
3.1.2.1. Selective pyrrole halogenation

In contrast to the readily available, well-known isomeric 2-acyl-4-halopyrroles,[70] synthetic routes towards the compounds **141** are few.[71] In the course of the research towards a scalable method for the preparation of these

70 P. Sonnet, J. Flippen, R. Gilardi, *J. Heterocycl. Chem*., **1974**, 11, 811.
71 B. Bray, P. Hess, J. Muchowski, M. Scheller, *Helv. Chim. Acta*, **1988**, 71, 2053.

compounds, most of the routes reported in literature were reviewed (Scheme 48).

Although direct halogenation of acylpyrroles **142** may lead to derivatives **141**, this method has limitations. Due to the electron withdrawing nature of the acyl substituent, direct halogenation always produces a mixture of isomers. The amount of the desired isomer **141** varies with the reaction conditions, but it is never the only product. Furthermore, it is often hard to separate the isomers. Also, because of complex coupling in the ^{1}H-NMR spectrum, the structures of 4-halo or 5-halo isomer have often been erroneously assigned,[77] and therefore, literature data have to be reviewed critically.



Scheme 48: Literature procedures to 5-halogenated acylpyrroles

After a review of the reported syntheses and a laborious optimization study, we concluded that a general and selective method for the syntheses of derivatives **141** would not be easy to establish based on halogenation of 2-acylpyrroles.

Lithiated azafulvenes **144** can be halogenated, and yield acyl derivatives upon hydrolysis.[72] Several different functional groups can be introduced in this way, but the acyl substituent is limited to formyl.

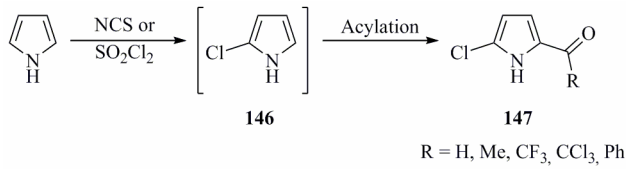
N-protected succinamidals **145** are reported to convert, in a Vilsmeier type reaction, to the 5-chlorinated pyrrole carbaldehyde.[73] Theoretically, other halogens and acyl substituents can be used. Nevertheless, this route failed in our hands, as no product was formed.

Another option would be to halogenate pyrrole first, using *N*-chlorosuccinimide, followed by acylation (Scheme 48).[71] The strong α-selectivity of pyrrole then ensures the correct regiochemistry. However, 2-halogenated pyrroles **143** are notoriously unstable and decompose violently

72 (a) S. Berthiaume, B. Bray, P. Hess, Y. Liu, M. Maddox, J. Muchowski, M. Scheller, *Can. J. Chem.*, **1995**, 73, 675; (b) P. Netchitaïlo, M. Othman, A. Daïch, B. Decroix, *Tetrahedron Lett.*, **1997**, 38, 3227; (c) G. Cordell, *J. Org. Chem.*, **1975**, 40, 3161.

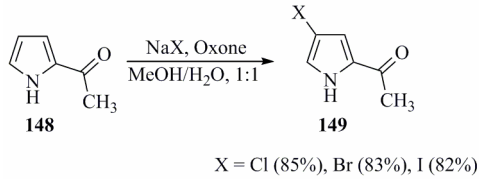
73 A. Guzman, M. Romero, J. Muchowski, *Can. J. Chem.*, **1990**, 68, 791.

upon attempts at isolation.[71] This seriously reduces the scope of the literature procedure. It is only after several attempts that a one-pot procedure could be developed (Scheme 49). Careful temperature control proved crucial to ensure selective and complete halogenation prior to in situ acylation.
Furthermore, the yield of the reactions is often significantly lowered due to incomplete halogenation. This can be avoided by using fresh *N*-chlorosuccinimide or changing instead to fresh sulfuryl chloride in dry THF. The sulfuryl chloride route is preferred, as halogenation is almost instantaneous, while the NCS route can take several hours to days to reach completion.
Fortunately, the Vilsmeier-Haack reaction,[74] trifluoroacetylation[75] and trichloroacetylation[76] proceeded smoothly in THF, furnishing the targeted 5-chlorinated acylpyrroles **147** on a large scale (up to 50 mmol) and with fair-to-good yields (33-64%).



Scheme 49. Synthesis of 5-chlorinated acylpyrroles

On the other hand, while repeating a reported procedure claiming to halogenate 2-acetylpyrrole at the 5-position in a methanol/water mixture with sodium halide/oxone (potassium peroxomonosulfate),[77] a single product was obtained. Instead of the reported structure of 5-halogenated isomer **147**, we found only the 4-isomer **149** to be formed in excellent yields after short reaction periods. Due to the typically small coupling constants (2-3 Hz) and meta-NH coupling, NMR-confirmation of the structure was ambiguous. From a detailed NMR-study and X-Ray evidence, the reaction was shown without any doubt, to yield exclusively the 4-halogenated isomer **149**. Chlorine, bromine and iodine can be introduced in yields between 80-95%. (Scheme 50).



Scheme 50. Oxone mediated 4-halogenation of 2-acetylpyrrole

74 J. White, G. McGillivray, *J. Org. Chem.*, **1977**, 42, 4248.
75 W. Peláeza, M. Burgos Paci, G. Argüello*, Tetrahedron Lett*., **2009**, 50, 1934.
76 D. Bailey, R. Johnson, N. Albertson, *Org. Syn., Coll. Vol*., **1988**, 6, 618.
77 E. Kim, B. Koo, C. Song, K. Lee, *Synth. Commun*., **2001**, 31, 3627.

3.1.2.2. Synthesis of the BODIPY dyes

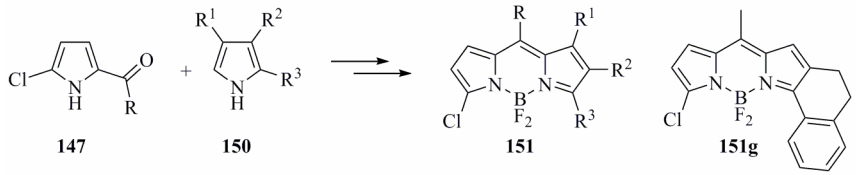
Once a selective synthesis of monohalogenated pyrroles **147** was established, they were converted to the BODIPY dyes (Scheme 51). This was accomplished by adding one equivalent of phosphorus oxychloride to a mixture of acylpyrrole **147** and a second pyrrole **150**.[2,5] The intermediate dipyrromethene was not isolated but was complexed *in situ* by adding excess triethylamine and boron trifluoride etherate to yield BODIPY dyes **151**. The BODIPY derivatives were then purified by column chromatography and were obtained in reasonable to good total yields (Table 3).

In this modular approach one can choose between several widely available pyrroles as the second moiety of the target BODIPY and this selection will significantly affect the properties of the resulting dye.

Furthermore, the nature of the acyl group can be changed to meet structural requirements. Through Vilsmeier-Haack acylation,[74] a 5-halogenated formylpyrrole and benzoylpyrrole were prepared. The use of reactive acid anhydrides or acid chlorides, allows trifluoroacetyl or trichloroacetyl to be introduced in good yield.

Applying these halogenated pyrroles in the previously established condensation approach then gives rise to an unsubstituted and a phenylated BODIPY dye (**151a** and **151c**), both in excellent yield. Trifluoroacetylpyrroles or trichloroacetylpyrrole do not participate in the reaction, and only lead to decomposition. As demonstrated by Burgess et al., a trifluoromethyl substituent has to originate from a condensation/oxidation approach (Scheme 28).

The major side product of the one pot condensation complexation reaction is scrambling of the pyrroles. In the case of aryl substituted pyrroles, the condensation is reversible, and this leads to a substantial amount of symmetric diarylated BODIPY dyes in the mixture. In these cases, careful use of apolar cosolvents, such as cyclohexane and pentane, can lead to a more efficient precipitation of the initial dipyrromethene and reduced scrambling.

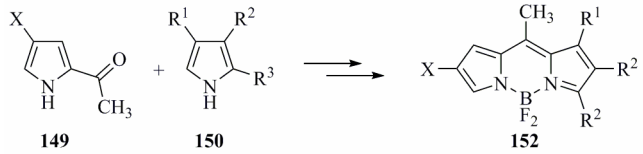


Scheme 51. Condensation of 5-halogenated acylpyrroles to 3-halogenated BODIPY dyes

Product	R	R^1	R^2	R^3	Yield (%)
151a	H	Me	H	Me	90
151b	Me	Me	H	Me	72
151c	Ph	Me	H	Me	43
151d	Me	H	Cyclohexyl		31
151e	Me	H	H	Ph	36
151f	Me	H	H	p-MeOPh	41
151g	Me	H	DHBI		30
151h	Me	H	C_5H_{11}	Me	55

Table 3. Results of structural variation in the condensation reaction towards 3-chlorinated BODIPY dyes

Since the 4-halogenated pyrroles **149** were available on large scale from our oxone mediated halogenation, they were also subjected to this condensation (Scheme 52). Unlike for the 5-halogenated isomer, also brominated and iodinated acylpyrroles can be prepared in high yield. Therefore, the corresponding halogenated boron dipyrrin complexes were prepared in multigram scale. Again, by changing the second pyrrole moiety, structural and spectral properties can be changed efficiently (Table 4).



149 **150** **152**

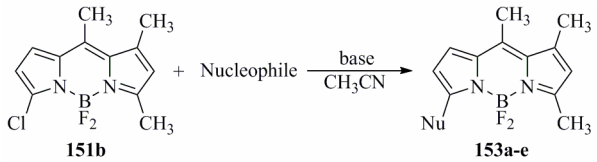
Scheme 52. Condensation of 4-halogenated acylpyrroles to 2-halogenated BODIPY fluorophores

Product	X	R^1	R^2	R^3	Yield (%)
152a	Cl	Me	H	Me	68
152b	Br	Me	H	Me	69
152c	I	Me	H	Me	74
152d	Br	H	DHBI		59
152e	I	H	DHBI		40
152f	I	H	H	Ph	25

Table 4: Results of structural variation in the condensation reaction towards 2-halogenated BODIPY dyes

3.1.2.3. Nucleophilic substitution

Just as for the 3,5 halogenated dyes,[46] the novel monochlorinated dyes **151** are susceptible to nucleophilic aromatic substitution (Scheme 53). Both for sulfur- and nitrogen-centered nucleophiles, gentle heating was required to speed up the reaction, and substituted products **153a** to **153d** could be obtained as crystalline solids in excellent yields (Table 5).
Substitution with oxygen nucleophiles was not as straightforward. Unlike the dichloro system, where substitution with phenolate or methoxide nucleophiles is rapid and clean, forcing conditions were unavoidable to acquire phenol ether **153e** in poor yield. Several attempts to introduce aliphatic alcohols *via* S_NAr were unsuccessful.



151b **153a-e**

Scheme 53. Nucleophilic aromatic substitution of a 3-chlorinated BODIPY

Product	Nucleophile	Yield
153a	$C_4H_9NH_2$	77
153b	$PhNH_2$	42
153c	C_4H_9SH	92
153d	PhSH	Quant.
153e	PhOH	16

Table 5: Various nucleophiles in S_NAr on model dye **151b**

We can partially attribute this diminished reactivity to the electron donating methyl substituents of the model system that seem to reduce reactivity towards nucleophiles.

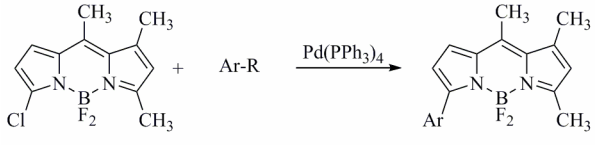
3.1.2.4. Palladium catalyzed reactions

The superior reactivity and selectivity of these monohalogenated dyes in palladium catalyzed reactions may be the largest advantage of the novel systems. They are susceptible to all of the most well known coupling procedures in moderate to excellent yields.

Suzuki coupling with boronic acids proceeds in high yield under standard conditions (Scheme 54).[78] Thus, refluxing in a mixture of toluene and

78 N. Miyaura, A. Suzuki, *Chem. Rev.*, **1995**, 95, 2457.

aqueous carbonate base provided the desired coupling products. Contrary to 3,5-dichloro-BODIPY dyes, no microwave irradiation was needed for an effective reaction. The use of microwave conditions even reduced the obtained yields, as substantial amounts of side products were formed. Despite clean reactions, long reaction times of up to 48h were sometimes required to force the reaction to completion under conventional heating.
More rapid reactions were observed with Stille coupling. The reaction of these substrates with organostannanes is generally very clean, and reactions can be finished within a few hours. Notwithstanding the high toxicity of organotin compounds, the ease of the Stille coupling is a big advantage.

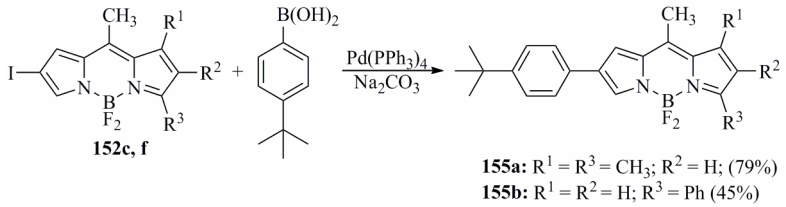


Scheme 54. Functionalization of a 3-chlorinated BODIPY dye **151b** using Suzuki-Miyaura and Stille coupling.

Reaction Type	Product	Ar	Yield
Suzuki	**154a**	Ph	65
	154b	*p*-*t*-Bu-Ph	93
	154c	*p*-F-Ph	51
	154d	2-Furyl	87
	154e	2-Thienyl	90
	154f	*p*-MeO-Ph	49
Stille	**154a**	Ph	74
	154e	2-Thienyl	66

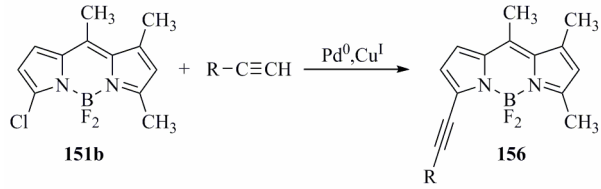
Table 6: Determination of the scope of the Suzuki and Stille coupling

In comparison to the Suzuki coupling at the 3-position, the analogous Suzuki reaction at the 2-position is less straightforward (Scheme 55). The increased electron density at this position makes it necessary to move to brominated or iodinated systems in order to observe reactivity. These reactions were less clean than for the 3-chlorinated isomers, and were accompanied by significant amounts of dehalogenation. Ultimately, several model systems were obtained (Scheme 55), both from a standard 5,7,8-trimethyl dye (**152c** to **155a)**, but also with red shifted asymmetrical fluorophores (**152f** to **155b)**.



Scheme 55. Functionalization of 2-halogenated BODIPY dyes using Suzuki-Miyaura coupling.

As the substitution of 3,5-dichloro-BODIPY **86** with phenylacetylene under Sonogashira conditions leads to some highly promising spectroscopic properties, such as a large red shift and a very high quantum yield of fluorescence,[53] we were keen to test this reaction on the novel 3-monohalogenated systems. By using standard conditions, *i.e.* tertiary amine base combined with catalytic amounts of copper iodide and palladium source, substitution of **151b** with phenylacetylene and trimethylsilylacetylene could be readily effected in moderate yields (Scheme 56).



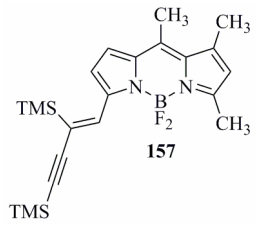
Scheme 56. Sonogashira reaction on model dye **151b**

Product	R	Base/Solvent (1:1)	Yield
156a	Ph	DIPEA/THF	46
156b	TMS	DIPEA/THF	48
156b	TMS	NEM/Dioxane	39
156c	TIPS	Et_3N/THF	58
156c	TIPS	NEM/Dioxane	70

Table 7. Highlighted examples from optimisation of Sonogashira reaction

The Sonogashira reaction mixture is always contaminated with an unexpected ene-yne by-product **157** from multiple alkyne complexation of the palladium complex. Despite prolonged efforts to elucidate the stereochemistry of the product through NMR methods or crystallization, no definite answer has been obtained. From a comparison with literature data,[79] the compound **157** is probably the *Z*-form, depicted in Scheme 57.

79 I. Stara, I. Stary, A. Kollarovic, F. Teply, D. Saman, P. Fiedler, *Tetrahedron*, **1998**, 54, 11209.

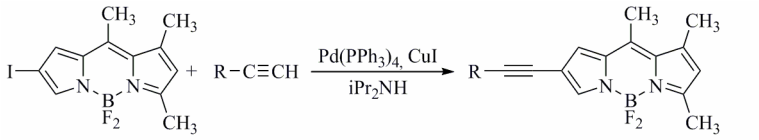


157

Scheme 57. Major side product found in Sonogashira coupling of 3-chlorinated BODIPY 151b

However, this problem can be solved through the use of triisopropylsilylacetylene (Table 7, entry 5), where the bulky substituent favours the elimination of the palladium complex and only traces of the side product can be observed.

The Sonogashira coupling can also be conducted at the 2-position (Scheme 58). Several examples thereof have been reported, but in all these cases, 1,3,5,7-methyl substituents were needed in order to get the correct regiochemistry.[59] No cosolvent is required, and as S_NAr is no side reaction, a secondary amine was selected. However, the catalyst loadings needed for the reaction are surprisingly low (<1%), as otherwise dehalogenation becomes a competing side reaction. The yields are generally good for the iodinated dye **152c**, but the brominated BODIPY **152b** reacts only slowly. No efforts were taken for further optimization of the protocol.



152c **158**

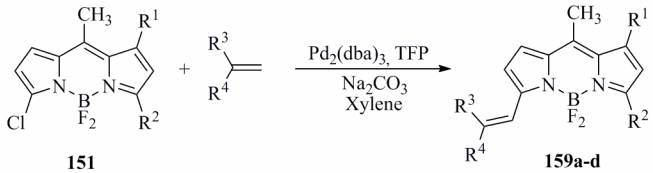
R = Ph (75%), TMS (81%), TIPS (79%)

Scheme 58. Sonogashira reaction of 2-iodinated BODIPY **152b**

Attempts to apply previously reported Heck procedures on BODIPY dyes **151b**, using DMF as a solvent and an amine base, to introduce double bonds were unsuccessful.[53] Although these conditions are highly suitable for several palladium catalyzed reactions on other systems, in our hands this only led to extensive decomposition and low yields of impure product.
A full optimization study ultimately resulted in a high yielding and clean procedure (Scheme 59). It seems that the key element is the use of mildly electron donating phosphine ligand trifurylphosphine (TFP) in apolar solvent. The highest yields were obtained in xylene at elevated temperatures and after acceptable reaction times. This procedure is also tolerant of

functional groups, and in this fashion, both styrene and an acrylate ester could be introduced in excellent yield (Table 8). Except for the model 5,7,8-trimethyl system **151b**, the reaction was also tested with dye **151f** in similar yields. The combination of both the styryl and the *p*-anisyl substituent in **159c** should lead to a strongly red shifted dye, as well as demonstrate the scope of the reaction.

It is important to note that these conditions are highly general, and can also be used for the Heck reaction on 3,5-dichlorinated BODIPY dyes (**86** to dye **101b** and **102b**).



Scheme 59. Heck reaction on 3-monochlorinated BODIPY fluorophores

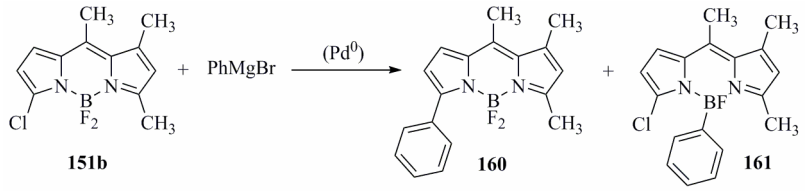
Product	R^1	R^2	R^3	R^4	Yield (%)
159a	Me	Me	H	Ph	93
159b	Me	Me	H	BuOOC	53
159c	H	p-MeO-Ph	H	Ph	78
159d	H	p-MeO-Ph	Ph	Ph	39

Table 8. Results of Heck reaction of several 3-halogenated BODIPY dyes

So far, no attempts have been made by our group to apply the Heck reaction to the 2-halogenated BODIPY dyes.

In search of even milder conditions for coupling reactions, the Kumada reaction was also tested, as this coupling of Grignard reagents and aryl halogenides can take place at room temperature. Reaction of the model compound **151b** with phenylmagnesium bromide generates an inseparable mixture of boron substituted product **161**, 3-carbon substituted **160** and products from multiple substitutions. Sadly, this is also the case for coupling of Grignard reagents under palladium(0) catalysis, the Kumada coupling (Scheme 60). Clearly, the reactivity of Grignard reagents is too high to get effective transition metal catalysis. Even though it is believed that alternatives for direct organometallic substitution such as the Negishi reaction[80] remain, no further efforts were made to attain optimized conditions.

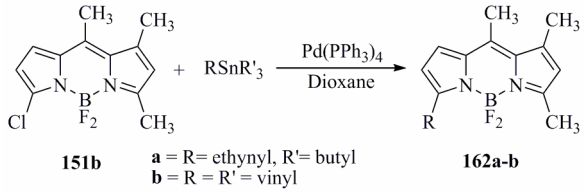
80 Prof. Dr. O. Riant, *Private communication*.



Scheme 60: Reactivity observed in Kumada reaction

3.1.2.5. 3-Ethenyl and 3-ethynyl as versatile reactive substrates

During this thorough study of palladium catalyzed coupling procedures, we also attempted to introduce a 3-ethynyl and 3-ethenyl substituent. These compounds could be substrates for several other reaction types, such as Heck reaction, Sonogashira reaction, click reaction, epoxidation etc.
As both substituents can be introduced through Stille reaction with corresponding stannanes, this reaction was tested first. Both ethenyl and ethynyl-stannanes coupled under palladium catalysis with the 3-chlorinated BODIPY dyes (Scheme 61), forming dyes **162a** and **162b**. The compounds have limited stability on silica, and are therefore best used immediately after preparation.

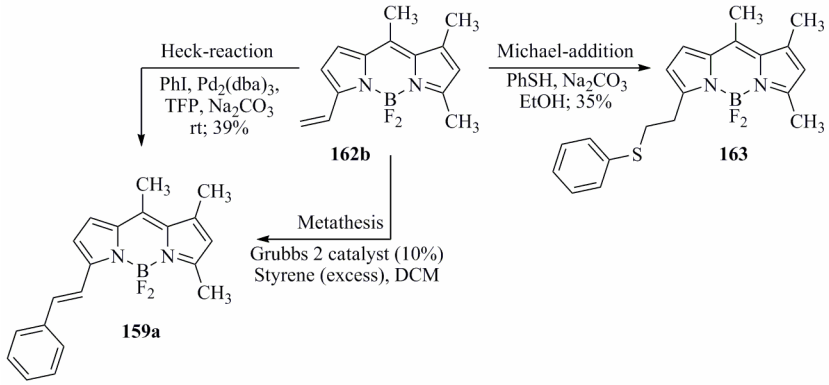


Scheme 61. Preparation of 3-ethenyl and 3-ethynyl BODIPY using Stille reaction

While the vinyl-BODIPY **162b** is a rather electron poor alkene, and the BODIPY can stabilize negative charges at the α-carbon such systems should be susceptible to Michael addition (Scheme 62). Thus, stirring the vinyl-BODIPY in ethanol in the presence of thiophenol leads to the formation of thioether **163** in moderate, unoptimized yield. Attempts to perform Michael addition with nitrogen nucleophiles were unsuccessful, probably due to reversibility of the reaction. The use of other nucleophiles is currently under investigation.

By subjecting the BODIPY alkene **162b** to Heck reaction protocols with iodobenzene, one can obtain the styrylated dye **159a**. Although these dyes can be prepared by regular Heck reaction with styrene on monochloro BODIPY **151b**, this inverted reactivity opens alternative opportunities to couple the BODIPY chromophore with halogenated aromatics.

Alkene metathesis, or the transalkylidenation between two alkene partners, has been used as a highly versatile method for the preparation of substituted alkenes.[81] Proof of concept for metathesis on our alkene BODIPY is the combination of styrene with vinyl-BODIPY in the presence of Grubbs 2 catalyst to **159a**.



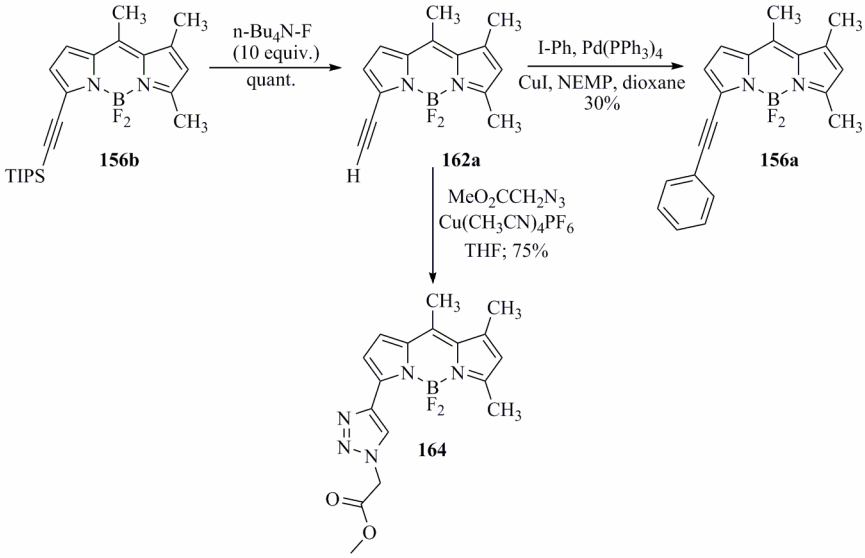
Scheme 62. Some transformations of the 3-vinyl-BODIPY dye (Yields are overall yields from **151b**)

Initially, the preparation of 3-ethynyl BODIPY **162a** was attempted through the deprotection of TMS-acetylene BODIPY **156b**. Deprotection with fluoride in THF at -78°C or methanolic OH^- at 0°C was very fast, but accompanied by extensive decomposition. Around this time, it was found that the use of TIPS-acetylene in the Sonogashira coupling provided cleaner reactions, and large amounts of protected 3-ethynyl BODIPY became available. Through a review of literature procedures for the deprotection of this TIPS-group, we found that the use of a tenfold excess of fluoride at room temperature resulted in clean and controllable formation of the desired compound (Scheme 63). Although this compound is not very stable, and decomposes over silica, an extraction procedure with standard workup furnishes the compound **162a** in near quantitative yield as a highly crystalline solid.

Even though the properties of this compound have not yet been fully determined, it shows some highly desirable reactivity.
Subjecting the compound to Sonogashira conditions with iodobenzene at room temperature provided coupling product **156a** in a moderate, unoptimized yield of 30%. Again, this approach is complementary to the one mentioned previously (Scheme 56), where a halogenated BODIPY is coupled with a terminal alkyne.

81 R. Grubbs, *Handbook of Metathesis*, Wiley-VCH, Weinheim, **2003**; R. Grubbs, S. Chang, *Tetrahedron*, **2004**, 54, 4413.

Furthermore, the unprotected alkyne is reactive in copper catalyzed cycloaddition with azides.[82] This reaction has been very popular in the last five years due to its scope and prominent place in the "click chemistry" philosophy.[83] Stirring the alkyne **162a** with methyl azidoacetate in THF at room temperature overnight with copper(I) tetrakis acetonitrile as catalyst, leads to 1,4-disubstituted-1,2,3-triazole **164**. Conducting the reaction at elevated temperatures results in more rapid formation of the product, and the reaction is finished after two hours at reflux temperature.



Scheme 63. Synthesis and modification of 3-ethynyl BODIPY **162a** (Yields are overall yields from **156b**)

82 (a) C. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem*., **2002**, 67, 3057; (b) M. Meldal, C. Tornoe, *Chem. Rev.*, **2008**, 108, 2952.

83 H. Kolb, M. Finn, K. Sharpless*, Angew. Chem, Int. Ed*., **2001**, 40, 2004.

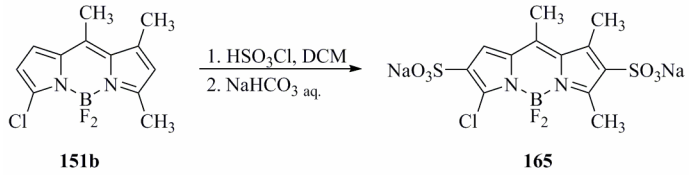
3.1.2.6. Post synthetic modification

After this extensive study into the synthesis and reactivity of monohalogenated BODIPY dyes, some efforts were undertaken to further substitute the boron dipyrrin scaffold. By doing so, the final fluorophore properties can be influenced.

Sulfonation

The group of Burgess recently reported an optimized protocol for both mono and disulfonation of 2,6-unsubstituted BODIPY dyes.[58] Sulfonates resulting from these reactions are highly water soluble, and can therefore be useful for biological applications. This water solubility in combination with the previously optimized reactivity can facilitate the introduction of our systems to this field of biological research.

Conducting this sulfonation reaction using a slightly modified literature procedure did furnish the disulfonated monochlorinated BODIPY **165**. Addition of chlorosulfonic acid to the 3-chlorinated model compound **151b** at -78°C, followed by basic hydrolysis, leads to the disulfonated product (Scheme 64). The compound can be purified with conventional methods and is a stable solid. It is both highly water soluble, and highly fluorescent. The properties of dye **165** towards nucleophilic substitution and palladium catalyzed reactions have not yet been studied.

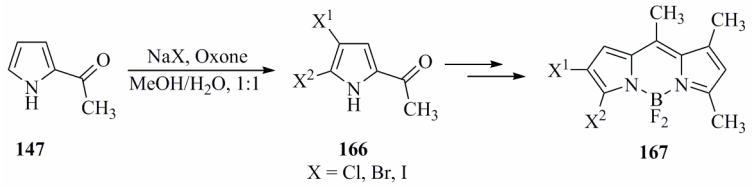


151b **165**

Scheme 64. Sulfonation of a monochlorinated model dye **151b** to enhance water solubility

Synthesis of selectively polyhalogenated BODIPY's

Through the use of the reactions established for the selective preparation of halogenated acylpyrroles, several new halogenation patterns can be achieved (Scheme 65). As mentioned previously, a high yielding synthesis of 4-halo-2-acetylpyrroles was established during the optimization of the 5-halo isomer. Further halogenation of such 4-halogenated pyrroles results in 4,5-dihalo pyrroles **166**, providing 2,3-halogenated BODIPY dyes **167** upon condensation/complexation.

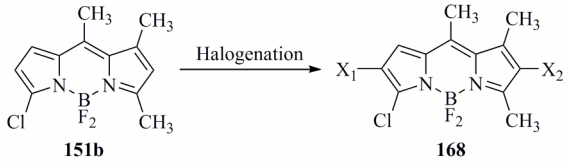


Scheme 65. Double halogenation of pyrrole for BODIPY dyes with 2,3-dihalogenation

Product	X^1	X^2	Yield (%)
167a	Br	Br	36
167b	Cl	Br	47
167c	I	I	35
167d	Cl	I	55

Table 9. Synthesis of BODIPY dyes with varied 2,3-dihalogenation

Electrophilic halogenation of 2- or 3-halogenated BODIPY dyes with the right directing methyl groups can result in the corresponding 2,3,6- or 3,6-polyhalogenated dyes (Scheme 66). Again, both iodination and bromination can be effected. The resulting dyes are stable, almost nonfluorescent solids, with poor solubility.



Scheme 66. Post condensation halogenation for complex halogenation patterns

Product	X^1	X^2	Yield (%)
168a	H	Br	54
168b	Br	Br	87
168c	H	I	65
168d	I	I	78

Table 10. Products and yields of direct halogenation of the BODIPY core

The major use of these halogenated systems is their application in the preparation of complex systems, optimizing both spectroscopic properties and introducing functionality. Research on this topic in relation with optimized sensitizers for photodynamic therapy is reported in section 3.7.2.

3.1.3. Spectroscopic properties

3.1.3.1. Variation of the pyrrole moieties

The variation in the prepared products is an ideal tool for an inquiry into the relationship between structure and spectroscopic properties (Table 11). Firstly, upon comparing *meso* substituents it is clear that a hydrogen and a methyl substituent (as in **151a** and **151b**, respectively) result in very similar properties. The methyl substituted compound **151b** has slightly blue shifted absorption spectra, but both of them have roughly the same quantum yields of fluorescence. A dramatic decrease of the quantum yield is observed when a phenyl substituent is placed at the 8-position (product **151d**). Even though it is sided by a methyl substituent, this does not seem sufficient to stop fast rotation of the aryl serving as a non radiative pathway of decay.

Concerning the substitution pattern on the second pyrrole moiety, the use of commercially available 2,4-dimethylpyrrole is convenient and leads to excellent features. Other pyrrole derivatives, however, are easily available, and the use thereof in the BODIPY preparation leads to profound changes in absorption and emission wavelengths.

Locking the alkyl substituents in a cyclohexyl ring **(151c)** results in a bathochromic shift in emission of roughly 20 nm, while retaining high quantum yields. This effect is quite extraordinary, and there is no obvious reason for it. However, the reduced conformational freedom is reflected in the lowered Stokes shift for the dye.

With aryl substituents at the 3-position (as in **151e** and **151f)** the conjugated system is extended, reflected in both red shifted absorption and emission. As the effect is more pronounced in the fluorescent emission, these compounds have an enlarged stokes shift. The introduction of an electron donating methoxy substituent in **151f** nearly doubles the shift induced by the aryl group.

Conformational restriction of the aryl groups leads to improved conjugation, and a large red shift, as can be observed in compound **151g**. Just as with the cyclohexyl fusion, the fluorescence in the restricted system is only slightly Stokes shifted.

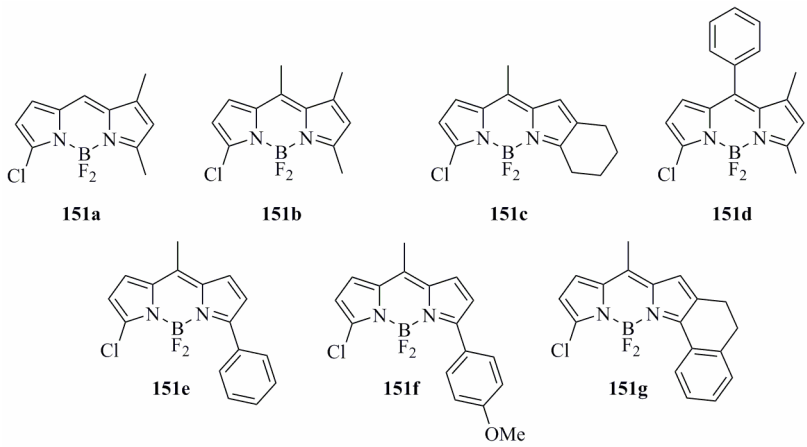


Table 11. Photophysical data of the 3-halogenated BODIPY dyes in several solvents

BODIPY	Solvent	λ_{abs} [a] / nm	λ_{em} [b] /nm	$\Delta\bar{\nu}$ [c] /cm^{-1}	Φ_f
151a	MeCN	496	509	515	0.74
	MeOH	498	509	434	0.81
	THF	501	512	429	0.87
	Toluene	507	517	382	0.76
151b	MeCN	488	503	611	0.73
	MeOH	490	504	567	0.76
	THF	493	506	521	0.89
	Toluene	499	512	509	0.80
151c	MeCN	514	527	480	0.69
	MeOH	515	527	442	0.78
	THF	517	529	439	0.92
	Toluene	523	534	394	0.86
151d	MeCN	495	511	633	0.015
	MeOH	496	512	630	0.014
	THF	499	516	660	0.21
	Toluene	503	520	650	0.031
151e	MeCN	519	544	885	0.61
	MeOH	522	545	808	0.85
	THF	526	550	830	0.99
	Toluene	532	555	779	0.91
151f	MeCN	534	565	1027	0.92
	MeOH	536	564	926	0.86
	THF	542	568	845	0.99
	Toluene	548	573	796	0.93
151g	MeCN	554	568	445	0.84
	MeOH	555	569	443	0.84
	THF	558	573	469	0.95
	Toluene	565	578	398	0.85

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift

When comparing absorption and emission profiles of the BODIPY dyes in function of their 5,6,7-substituents, almost full coverage of the visible spectrum can be observed (Figure 1). By using these starting compounds and variations thereof, dyes with colours from green to red are available for future modification and labelling.

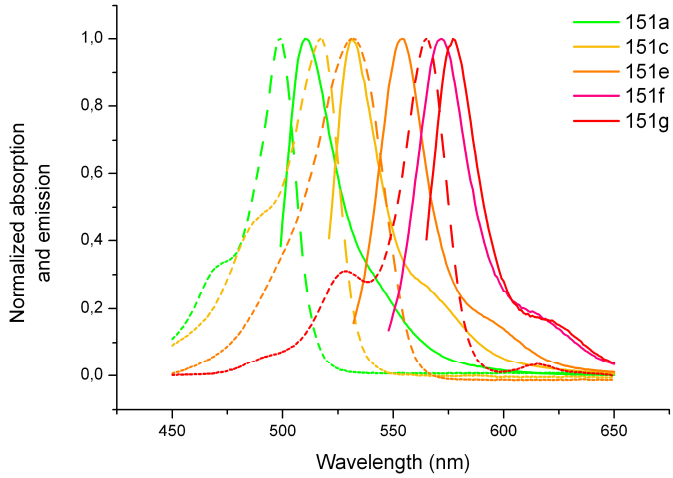


Figure 1. Normalized absorption and emission profiles of the 3-chlorinated BODIPY dyes **151a-g** in Toluene

With exception of *meso*-arylated dye **151d**, the quantum yield of these fluorophores is relatively independent of solvent polarity. In a small but definite trend, one can see that the quantum yield is the highest in THF in all cases.

3.1.3.2. Nucleophilic substitution

The placement of heteroatoms at the 3,5-positions has been shown to change the spectral properties of the resulting BODIPY profoundly. With the notable exception of oxygen substituents, all products have absorption and emission spectra that are strongly red-shifted (Table 1).
As described previously,[48] oxygen substituents at the 3-positions do not lead to the bathochromic shifts seen in other nucleophiles. The red shift in **153e** remains limited to approximately 8 nm in both absorption and emission, while Stokes shift and quantum yields are virtually unchanged.
For the introduction of a nitrogen nucleophile, a red shift is observed for absorption (~20 nm), but the fluorescence emission of the dye is even further bathochromically shifted. This difference is reflected in the Stokes shift, which is rather large for these dyes. The planarity of the systems and the lack of rotating moieties lead to quantum yields that are relatively high. Unlike the 8-tolyl-3-anilino-BODIPY **87a** the quantum yield of fluorescence is not especially solvent dependent. This indicates that there is no substantial donor-acceptor interaction from the amine into the electron poor BODIPY system.
In sulfur substitution **153c**, a slightly larger red shift than for the aminated dye **153a**, can be correlated with a smaller Stokes shift, indicating that also the absorbance is more red shifted in this case. As was observed in previous studies, the sulfide dyes have very high quantum yields.

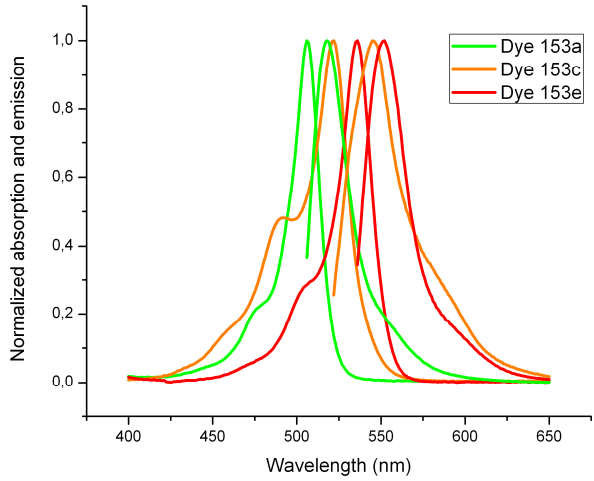
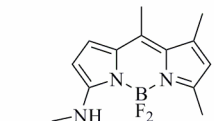
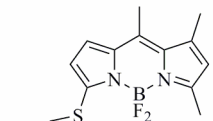


Figure 2. Normalized absorption and emission profiles of the butylamine, butylthiol and phenol substitution products of **151b**, indicating their distinct properties (Toluene)

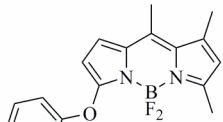
Table 12. Photophysical data of the products from nucleophilic aromatic substitution in several solvents



153a



153c



153e

BODIPY	Solvent	λ_{abs} [a] / nm	λ_{em} [b] /nm	$\Delta\bar{\nu}$ [c] /cm^{-1}	Φ_f
153a	MeCN	508	540	1167	0.64
	MeOH	510	538	1020	0.62
	THF	514	543	1039	0.78
	Toluene	522	546	842	0.73
153c	MeCN	525	544	665	0.83
	MeOH	527	545	627	0.86
	THF	530	549	653	1.00
	Toluene	536	553	574	0.88
153e	MeCN	497	511	551	0.67
	MeOH	499	512	509	0.70
	THF	501	515	543	0.85
	Toluene	506	519	495	0.72

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift

3.1.3.3. Palladium catalyzed functionalization

The introduction of new substituents *via* palladium catalyzed reactions prompts bathochromic shifts in the absorption and emission spectra, and the spectral characteristics of the products obtained are listed in Table 13.

With 3-(*p*-(*t*-butyl))phenyl-BODIPY **154b** as the standard, it is clear that the 4-fluorofenyl substituent in **154c** has little effect. The electron withdrawing substituent shifts the absorbance and emittance slightly hypsochromically, but the compound is still highly fluorescent.

As witnessed in the chlorinated dyes (Table 12), an electron donating substituent induces an extra red shift. The electron rich five membered rings thiophene and furan (in **154d** and **154e**) bring about a similar red shift, but have small Stokes shifts when compared to phenylated systems. These interesting properties, combined with the fact that the 5-membered heterocycles can be introduced in very high yield, makes them excellent fluorescent probes for further use.

Oddly enough, *p*-anisyl substituted dye **154f** suffers from a relatively low quantum yield. There is no obvious reason for this, and this contradicts the results obtained for dye **151f**.

Double bond containing BODIPY dyes **159a** and **159b** are also highly fluorescent. The extended conjugation of the styrene in relation to acrylate **159a**, is reflected in an extra bathochromic shift of ~23 nm.

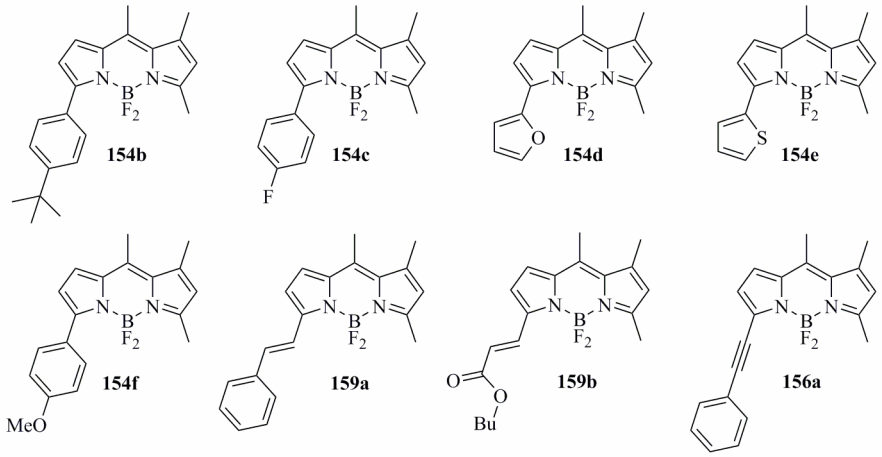


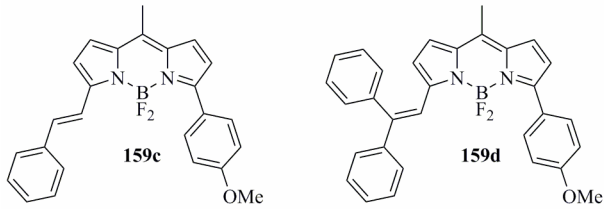
Table 13. Photophysical data of the products from palladium catalyzed substitution in several solvents

BODIPY	Solvent	λ_{abs} [a] / nm	λ_{em} [b] /nm	$\Delta\bar{\nu}$ [c] /cm^{-1}	Φ_f
154b	MeCN	513	543	1077	0.85
	MeOH	517	545	994	0.79
	THF	522	549	942	0.86
	Toluene	527	553	892	0.83
154c	MeCN	507	538	1137	0.50
	MeOH	510	539	1055	0.64
	THF	515	543	1001	0.80
	Toluene	520	546	916	0.61
154d	MeCN	542	565	751	0.83
	MeOH	545	567	712	0.82
	THF	549	569	640	0.97
	Toluene	556	573	534	0.85
154e	MeCN	537	562	828	0.82
	MeOH	541	562	691	0.86
	THF	547	566	614	0.92
	Toluene	554	570	507	0.84
154f	MeCN	520	558	1310	0.20
	MeOH	528	560	1082	0.36
	THF	529	565	1204	0.65
	Toluene	535	565	992	0.25
159a	MeCN	548	562	455	0.81
	MeOH	549	564	484	0.89
	THF	554	567	414	0.98
	Toluene	559	571	376	0.85
159b	MeCN	525	540	529	0.56
	MeOH	527	541	491	0.93
	THF	531	543	416	1.00
	Toluene	536	548	409	0.85
156a	MeCN	525	545	699	0.77
	MeOH	530	548	620	0.85
	THF	535	551	543	0.93
	Toluene	542	556	465	0.93

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift

As mentioned earlier, Heck reaction did allow us to reach a triply substituted styrene dye. Both as an example of the scope of the reaction and the concomitant red shift, a *p*-methoxy-phenyl substituent was placed at the 5-position (Table 14).
In line with the expectations, the additional phenyl substituent on the double bond (**159d**) led to an additional red shift, but presumably due to ineffective conjugation the shift was only 11-12 nm.

Table 14. Photophysical comparison of the double and triple substituted styrene dyes **159c** and **159d**



BODIPY	Solvent	λ_{abs} [a] / nm	λ_{em} [b] /nm	$\Delta\bar{\nu}$ [c] /cm^{-1}	Φ_f
159c	MeCN	588	618	826	0.67
	MeOH	591	619	765	0.56
	THF	596	624	753	0.67
	Toluene	603	627	635	0.48
159d	MeCN	595	629	908	0.70
	MeOH	598	630	849	0.78
	THF	604	636	833	0.92
	Toluene	611	639	717	0.84

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift.

3.1.3.4. Effect of the position of functionalization

A notable advantage of this modular condensation approach is the ability to introduce functionalities at different positions of the BODIPY core. Functionalization at these positions may well have distinct effects on the spectroscopic properties, and up to now, no systematic study of these influences had been reported.

However, functionalization at the 3-position is believed to be of particular interest and therefore we looked into a deeper comparison with the 2-position, using the phenylacetylene substituted products.

When comparing the absorption and emission profiles of the isomeric products **156a** and **158a**, it is immediately clear that the two chromophores behave quite different. From a solvent study of the quantum yield of both dyes in a range of solvents, one can see that the 3-alkyne isomer has higher quantum yields in all solvents. The quantum yield of fluorescence ranges between 0.78 and 0.95, and it is relatively solvent independent. The quantum yield of the 2-isomer is more dependent on the solvent polarity, ranging from 0.35 to 0.75.

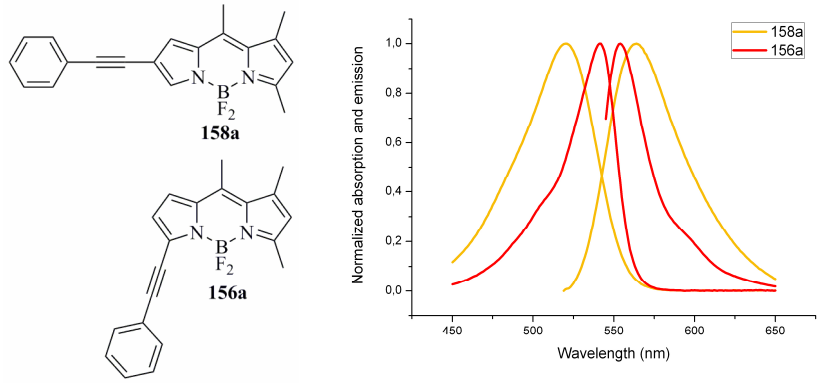


Figure 3. Structure of the 2- and 3-phenylethynyl-BODIPY, and their normalized absorption and emission in toluene

BODIPY	Solvent	λ_{abs} [a] / nm	λ_{em} [b] /nm	$\Delta\bar{\nu}$ [c] /cm^{-1}	Φ_f
156a	MeCN	525	545	699	0.77
	MeOH	530	548	620	0.85
	THF	535	551	543	0.93
	Toluene	542	556	465	0.93
158a	MeCN	503	566	2213	0.25
	MeOH	507	566	2056	0.37
	THF	513	569	1918	0.50
	Toluene	521	561	1369	0.61

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift.

The 2-isomer absorbs at shorter wavelengths (503 nm to 521 nm) than the 3-phenylacetylene-BODIPY (525 nm to 542 nm), but nonetheless emits higher (545 nm to 556 nm for **156a**, compared to 561 nm to 569 nm for **158a**).
The molar extinction coefficient of the 3-substituted product is 58850 in chloroform and 49295 in methanol. With brightness defined as the product of molar extinction coefficient and quantum yield,[84] this results in brightnesses of 47080 and 49295 lmol^{-1}cm^{-1}, in methanol and in chloroform respectively. For the 2-isomer, molar extinction coefficients are lower, 30186 in chloroform and 29738 in methanol. Combined with their lower quantum yields, the respective brightnesses are significantly reduced compared to the 3-isomer, counting only 18413 in chloroform and 11300 in methanol. The bandwidth of the 3-isomer is about half that of the 2-isomer.
These data support our premise that 3-substitution is indeed a highly beneficial method of derivatisation, resulting in high quantum yields and molar absorption coefficients.

84 S. E. Braslavsky, *Pure Appl. Chem.*, **2007**, 79, 293.

3.1.4. Conclusion

Through the establishment of synthetic routes to selectively halogenated pyrroles, a highly versatile modular condensation approach to halogenated BODIPY dyes is reported. These spectral properties of these dyes can be modified through a careful choice of the second pyrrole moiety.
The reactivity of the fluorophores has been thoroughly investigated, and is shown to be remarkably flexible. Combining both the adaptable synthesis and functionalization, dyes with absorption and emission throughout the visible spectrum can be obtained.

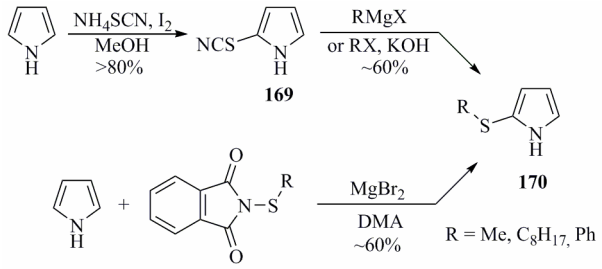
3.2. Sulfur-Halogen systems for orthogonal functionalization

3.2.1. Synthesis

Sulfur containing groups can act as powerful pseudohalogens, undergoing both nucleophilic substitution and palladium catalyzed coupling reactions.[66,67,68]

Despite the obvious method of introducing these sulfur groups by nucleophilic substitution of a halogen atom being published by the groups of Dehaen,[46] Burgess,[51,58] Bane,[49,50] and Vosch,[48] a condensation approach has not yet been introduced to the field.

The preparation of pyrrolic thioethers **170** and their respective acylpyrrole derivatives is well known in pyrrole chemistry (Scheme 67). In our hands, starting with thiocyanation and subsequent ether formation initially deemed to be the best option. Base mediated decyanation followed by thioether formation was rapid, and can be effected both by adding Grignard reagents to a thiocyanopyrrole,[85] or KOH and an alkyl iodide.[86] However, following a recent report by Thompson,[87] the preparation and use of sulfenyl phthalimide as sulfanylation reagent proved to be an elegant and high yielding one step method. This reaction affords the desired pyrrole thioethers in an easy sulfanylation procedure with $MgBr_2$ as a catalyst in DMA.



Scheme 67. Routes to sulfanylpyrroles

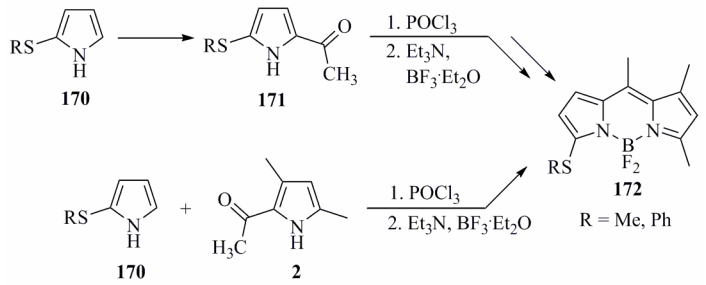
Acid catalyzed condensation of these electron rich pyrroles **170** with substituted acylpyrrole **2**, or of the corresponding acylpyrroles of thioether

85 P. Thamyongkit, A. Bhise, M. Taniguchi, J. Lindsey, *J. Org. Chem*., **2006**, 71, 903.

86 O. Carmona, R. Greenhouse, R. Landeros, J. Muchowski, *J. Org. Chem*., **1980**, 45, 5336.

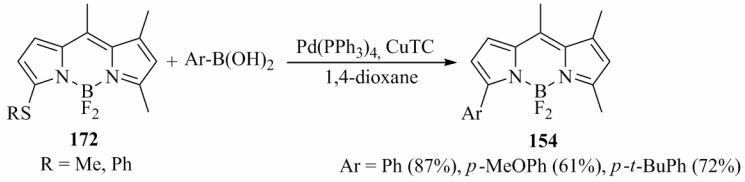
87 (a) H. Gilow, *Tetrahedron Lett*., **1986**, 27, 4689; (b) M. Gillis, L. Greene, A. Thompson, *Synlett*, **2009**, 112.

pyrroles **171** with a second pyrrole, rapidly leads to the dipyrrin dyes, and complexation with boron trifluoride then yields the highly fluorescent sulfanylated BODIPY dyes **172** (Scheme 68). Both routes suffer from scrambling, as both pyrrole moieties are electron rich and the reaction is very fast but reversible, forming the symmetrical products as well. By controlling the solubility and the reaction time, side product formation is limited and the products can be separated chromatographically.



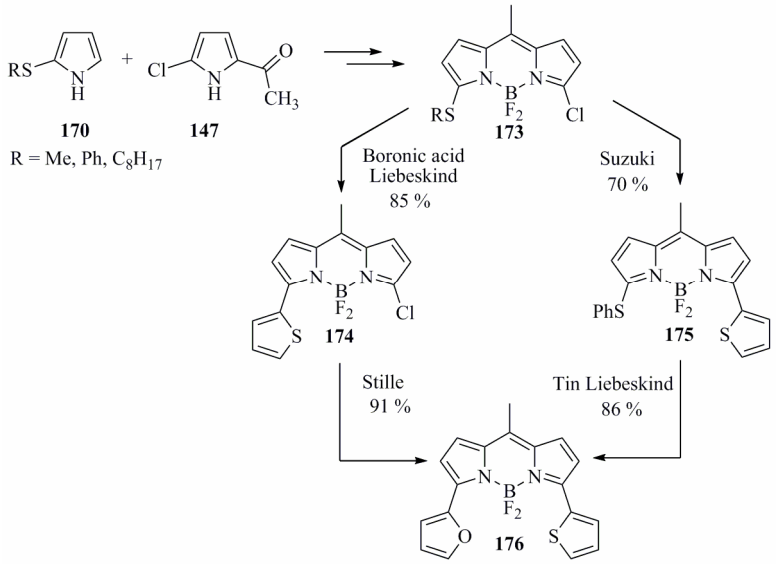
Scheme 68. Condensation of sulfenylpyrroles to yield 3-sulfanyl-BODIPY dyes

The most efficacious use of these thiolated systems **172** is the use in Liebeskind-Srogl coupling. The latter is orthogonal to convenient arylation reactions,[68] such as Suzuki and Stille coupling. Rapid coupling under base free conditions is easily established by adapting standard substitution conditions (Scheme 69). A simple change from refluxing THF to dioxane is sufficient to eliminate the need for an excess of boronic acid, and yields arylated dyes **154** in good yield.



Scheme 69. Liebeskind reaction on 3-sulfanylated BODIPY dyes

Obviously, the use of our 5-halo-2-acylpyrroles **146** in a condensation with thioether pyrroles **170** furnishes the hybrid 3-chloro-5-thioether-BODIPY fluorophores **173**. Such systems can be selectively substituted with both the standard coupling reactions on halogens, Suzuki coupling using boronic acids and Stille coupling using tin reagents (Scheme 70). The thioether groups show complementary reactivity as Liebeskind reactions of both boronic acids and stannanes proceed in high yield. Indicative of the power of this orthogonal approach is the formation of an asymmetric heteroarene substituted BODIPY **176** through two reaction sequences, all proceeding in impressive yield and fully orthogonal. Similar to previously mentioned systems, 3-(2-thienyl) BODIPY **154d** and 3(2-furyl) BODIPY **154c**, such electron rich substituents effect a large red shift on the dye (See Table 13).



Scheme 70. Synthesis and substitution of 3-chloro-5-sulfanyl-BODIPY dyes, showing full orthogonality in transition metal catalyzed coupling.

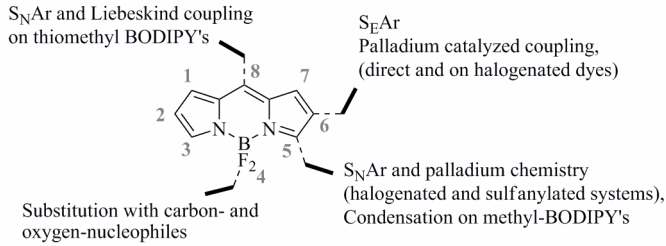
3.2.2. Conclusion

A new condensation approach to sulfanyl boron dipyrrin dyes is disclosed. Pyrrole thioethers are more stable than their halogenated counterparts, and therefore allow more convenient handling. The sulfanyl BODIPY dyes are susceptible to palladium catalyzed coupling in the Liebeskind reaction. Furthermore, by combining the thioethers with building blocks from our selective halogenation approach, hybrid systems were obtained. These systems show full orthogonality in palladium chemistry, and can be reacted in superior yields.

3.3. 1,7-Disubstituted BODIPY fluorophores

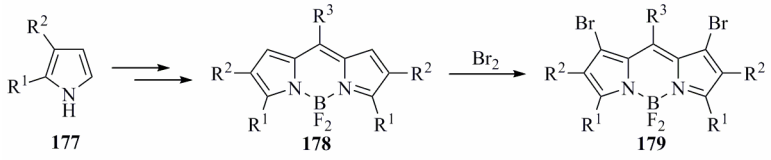
3.3.1. Introduction and synthesis

After analysis of the literature data on reactive BODIPY dyes, it is clear that substitutions at almost all positions have been investigated (Scheme 71). While palladium catalyzed cross coupling has been described for the positions 2, 3, 4, 5, 6 and 8, nucleophilic substitution of halogens and thioethers is reported for positions 3, 4, 5 and 8. As such, the only reactivity that remains uncharted is 1,7-substitution.



Scheme 71. Classification of reactive BODIPY dyes by position and reported functionalization

Therefore, we set out to prepare and evaluate 1,7-disubstituted BODIPY dyes. However, this position has no distinct activation mechanism, and is therefore the last to be halogenated in the direct electrophilic halogenation of a BODIPY dye. The use of this approach can only be effective through blockage of all the other positions.
Such 2,3,8-trisubstituted dyes can be conveniently prepared through standard BODIPY preparations with substituted pyrroles. Both 2,3,5,6-tetramethylated and restricted *bis*(dihydrobenzindole) dyes **178** were obtained in moderate yields, and subjected to halogenations studies.
It was clear that halogenations can be effected with standard halogenating agents, and both monobrominated (not shown) and dibrominated dyes **179** were isolated (Scheme 72). Direct iodination is also possible, but the resulting compounds are exceedingly difficult to purify.



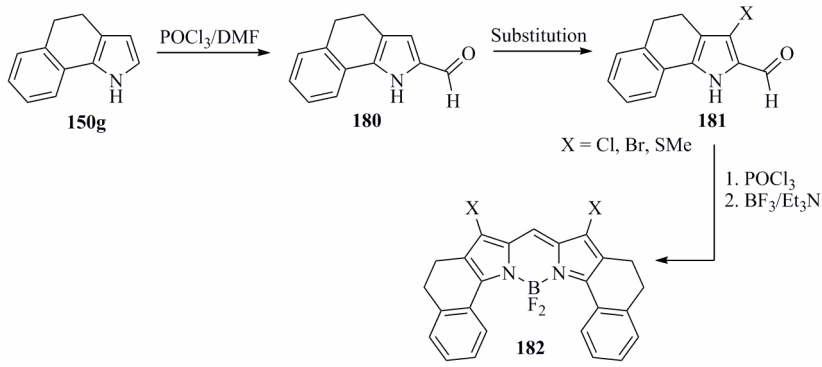
Scheme 72. 1,7-halogenation of BODIPY dyes

Product	R^1	R^2	R^3	Yield[a]	Yield[b]
179a	CH_3	CH_3	CH_3	19	82
179b	CH_3	CH_3	CH_3	-	44
179c	CH_3	CH_3	Ph	27	-
179e	DHBI		CH_3	36	Quant.

a) Yield for condensation, from pyrrole **17**; b) Yield for bromination

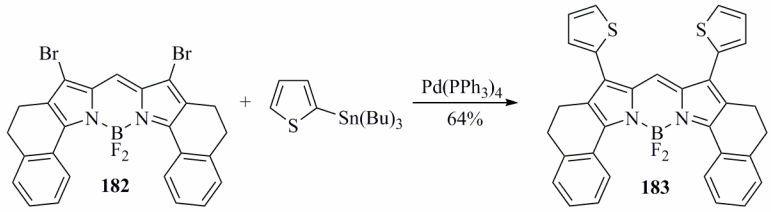
Initial attempts to subject these systems to palladium catalyzed cross coupling reactions showed that reactions were accompanied by hydrodehalogenation, and the resulting reaction mixtures could not be purified. These side reactions occurred under the previously optimized Suzuki, Stille and Sonogashira protocols. As steric crowding of the intermediate palladium complex was reasoned to be the origin of this hydrodehalogenation, we turned our attention to *meso*-unsubstituted systems.

In this case, halogenation of the *meso* position would intervene, so halogenation at the pyrrole stage was desirable. Furthermore, placing a hydrogen substituent on the 8-position would require working with aldehydes. From these premises, a strategy was designed that would use the one pot condensation described earlier by Burgess (Scheme 73).
Dihydrobenzindole **150g** was formylated in high yield using Vilsmeier conditions, setting the stage for halogenation studies. By using standard pyrrole halogenation protocols,[74] chlorinated and brominated derivatives **181** were isolated as highly crystalline solids.
We were also interested in the possibility of thiolation at this stage, and subjecting these thioethers to the one pot phosphorus oxychloride mediated condensation. By applying both of the pyrrole sulfanylation sequences mentioned previously, the desired thioethers were obtained. However, thiocyanation with ammonium thiocyanate and iodine in methanol was low yielding, and direct sulfanylation with phthalimide reagents was therefore preferred.
Much to our delight, we observed clean and rapid formation of deep blue 1,7-dihalogenated and 1,7-bis-methylsulfanyl BODIPY dyes **182** in excellent yields



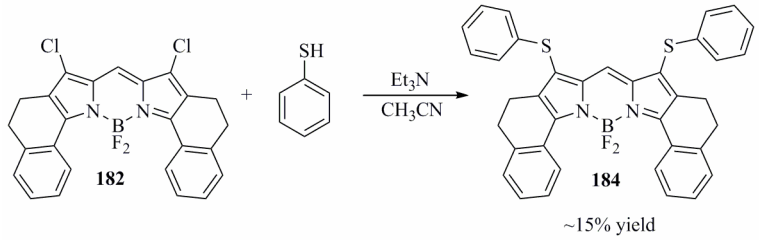
Scheme 73. Halogenation-condensation approach to 1,7-reactive BODIPY fluorophores

Research into palladium catalyzed reactions on these substrates is currently ongoing, but indicatory of their feasibility is the incorporation of two thiophene units in a Stille reaction to BODIPY **183** (Scheme 74). This compound is a 1,7-disubstituted analogue of 3,5-*bis*-thienyl-BODIPY dyes that are currently studied for their use in fluorescent polymers. Also, further investigation of nucleophilic aromatic substitution, as well as an evaluation of the spectroscopic properties is currently ongoing.



Scheme 74. Stille reaction on 1,7-dibrominated BODIPY dye

The reactivity towards nucleophiles is low. Prolonged heating of the dichlorinated dye in acetonitrile in the presence of butylamine did not lead to amine substitution. However, reaction was observed with sulfur nucleophiles (Scheme 75). Reflux with an excess of thiophenol in basic acetonitrile did allow the *bis* sulfanylated dye **184** to be isolated in low yield, as an intensely green dye. The monosubstituted product could be observed, but we were unable to separate it from remaining starting material. Again, more research is needed to reach optimized conditions.



Scheme 75. Nucleophilic substitution of 1,7-dichloro BODIPY by thiophenoxide.

3.3.2. Conclusion

The initial design based on halogenation of heavily substituted dyes had to be revised, as substitution of these halogenated BODIPY's was accompanied by side reactions. By using an inventive condensation approach, reactive systems with less steric crowding were reached. From initial studies, these fluorophores seem to meet the expected reactivity. As these reactions start from dyes emitting deep in the red, substitution is expected to lead to a new range of near infrared fluorescing BODIPY dyes.

3.4. Palladium catalyzed heterocycle formation towards restricted dyes

3.4.1. Introduction to rotationally restricted BODIPY dyes

Since the appearance of BODIPY dyes in the late 1960's, considerable effort has been put in the extension of their favourable spectroscopic properties to longer wavelengths. The search for bright fluorophores that absorb and emit in the red visible (vis) to the near infrared (NIR) spectral range continues incessantly. Stable dyes with sharp absorption and fluorescence emission bands in the red or NIR region of the spectrum, combined with high molar absorption coefficients $\varepsilon(\lambda)$ and high fluorescence quantum yields Φ_f, may find extensive use in many different fields, such as optical engineering, analytical chemistry, biological *in vivo* imaging and sensing applications, and material science.

Extension of the conjugated system is the most widely used method to obtain BODIPY dyes with spectra shifted to longer wavelengths. Conveniently, this can be established by substitution of the BODIPY core with aromatic groups.[88,53] 3,5-Diaryl substituted BODIPY dyes can show a bathochromic shift of over 100 nm, but generally have low to moderately high fluorescence quantum yields Φ_f due to nonradiative decay via rotational relaxation caused by the aromatic substituents. The introduction of alkenyl substituents produces even larger bathochromic shifts and the rigidity of the double bond generally results in higher Φ_f values. [27, 28, 53] Alkyne substitution at the 3(,5)-position(s) produces interesting BODIPY fluorophores with high quantum yields and large red shifts.[89]

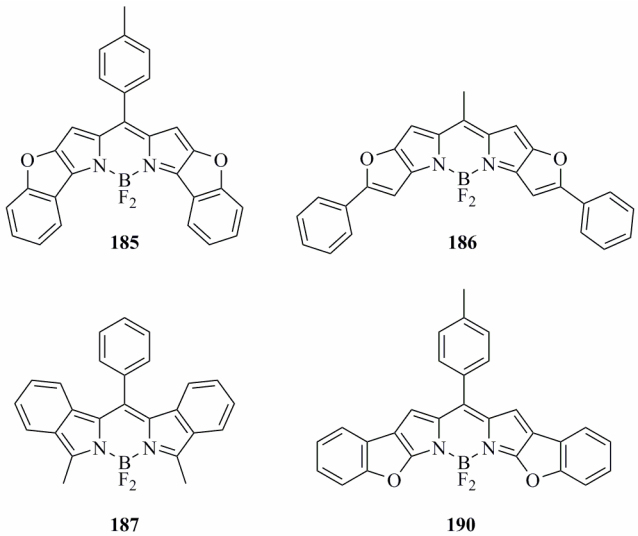
Annulation, i.e., the building of a ring onto some starting molecule can be used to extend the ring system and reduce the nonradiative decay via rotational relaxation and hence to enhance fluorescence. Building of heterocyclic rings onto the aromatic rings attached to the BODIPY core can even lead to NIR emitting dyes. Burgess et al. described that conformationally constrained, aryl-substituted BODIPY dyes **185** have longer absorption and fluorescence emission maxima, higher $\varepsilon(\lambda)$ and Φ_f values than the unconstrained BODIPY dyes.[90] Ono et al. reported the

88 (a) L. Thoresen, H. Kim, M. Welch, A. Burghart, K. Burgess, *Synlett*, **1998**, 1276; (b) A. Burghart, H. Kim, M. Welch, L. Thoresen, J. Reibenspies, K. Burgess, F. Bergström, L. Johansson, *J. Org. Chem*., **1999**, 64, 7813.

89 V. Leen, E. Braeken, K. Luckermans, C. Jackers, M. Van der Auweraer, N. Boens and W. Dehaen, *Chem. Commun.*, **2009**, 30, 4515.

90 J. Chen, A. Burghart, A. Derecskei-Kovacs, K. Burgess, *J. Org. Chem*., **2000**, 65,

synthesis and optical properties of BODIPY dyes fused with rigid bicyclo rings, which were converted quantitatively into aromatic ring fused derivatives **187** by means of a retro Diels-Alder reaction, thus avoiding unstable isoindole intermediates.[91] A series of bright furan–BODIPY fused dyes **186**, dubbed KEIO fluors, have very large $\varepsilon(\lambda)$ and high Φ_f values and show fluorescence emission spectra in the Vis–NIR region that are extremely sharp. The preparation of all these reported, rigid BODIPY dyes required lengthy multi-step syntheses of the ring fused pyrroles as starting materials. Intrigued by these reports on fluorescent dyes with extended conjugation and restricted bond rotations, we designed a convenient and highly efficient two-step synthetic route to BODIPY derivatives fused with rigid benzofuran units. The advantages of this synthetic strategy are two-fold: (i) this synthesis eliminates the tedious preparation of ring fused pyrroles, (ii) through this sequential ring formation reaction, a nonsymmetric dye is easily accessible.



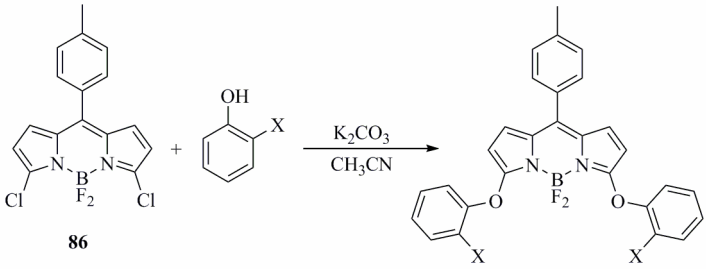
Scheme 76. Some examples of rigidified BODIPY dyes, discussed in this study

2900.

91 (a) M. Wada, S. Ito, H. Uno, T. Murashima, N. Ono, T. Urano, Y. Urano, *Tetrahedron Lett.*, **2001**, 42, 6711; (b) Z. Shen, H. Röhr, K. Rurack, H. Uno, M. Spieles, B. Schulz, G. Reck, N. Ono, *Chem. Eur. J.*, **2004**, 10, 4853.

3.4.2. Synthesis

As reported in our earlier work, 3,5-dichlorinated BODIPY dyes can be substituted efficiently by a variety of nucleophiles. Thus, nucleophilic aromatic substitution of 3,5-dichloro-BODIPY **87** with 2-bromophenol and 2-iodophenol takes place readily and in near quantitative yield, furnishing the desired starting materials **188** and **188b** in gram scale (Scheme 77).



Scheme 77. Nucleophilic substitution of dichloro-BODIPY **87**with ortho-halogen phenol nucleophiles.

Proper positioning of a halogen (X = Br or I) atom on the phenyl ring should make the system susceptible to benzofuran ring formation. Transition metal catalyzed ring formation has found widespread use in the synthesis of heteroaromatic systems.[92] In these reactions, the metal of choice is mostly palladium. The reaction mechanism involves an oxidative insertion of Pd(0) into the carbon-halogen bond, followed by rapid insertion into the neighbouring unsaturated system and subsequent reductive elimination.
Initial experiments with Pd(0) sources proved the viability of our premise: the closed products **189** and **190** were being formed after prolonged heating (7 days) and in low yield (Scheme 78). Often these reactions are carried out in polar solvents, like DMF (*N,N*-dimethylformamide), DMA (*N,N*-dimethylacetamide) or NMP (*N*-methylpyrrolidone), to increase the reaction rate. Although fast reaction was observed in these solvents, the products had limited stability under these conditions. As optimized reaction conditions we used Pd(II) precatalysts and the long reaction times could be reduced to two days (Table 15). Even with microwave irradiation (entry 10, MW), the reaction still took 8 hours to go to completion. This microwave procedure led to the ring-closed product **190** in excellent yield. Interestingly, stopping the reaction before completion allowed us to isolate the intermediate BODIPY dye **189**. There is no significant difference in reactivity between the first ring formation and the second: compound **189** was separated in 32% yield from a mixture of starting material **188** and dye **189**. The use of a

92 G. Zeni, R. Larock, *Chem. Rev*., **2006**, 106, 4644.

nickel catalyst under similar conditions did not result in the desired ring formation. Also, the use of 2-iodophenol instead of 2-bromophenol did not produce drastic changes. As expected, reactions were faster when using iodinated dye **188b**, and the isolated yield was slightly higher.

Scheme 78. Transition metal catalyzed benzofuran formation.

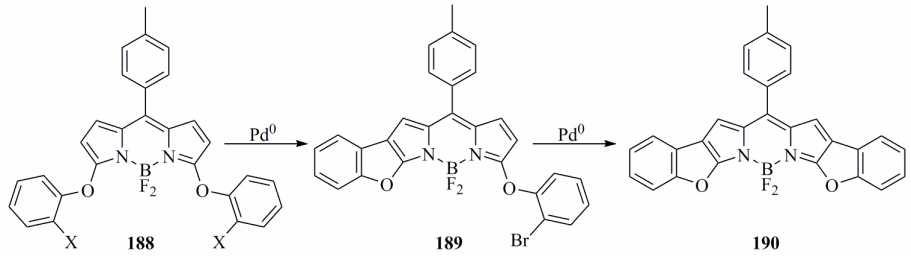


Table 15 Reaction conditions of transition metal catalyzed annulation.

Catalyst[a]	Solvent	Ligand	Base	Time	X	Temp (°C)	Yield (%) [b]
$Pd(PPh_3)_4$	THF	PPh_3	K_2CO_3	7 days	Br	78	12
$Pd(PPh_3)_4$	DMF	PPh_3	K_2CO_3	18 h	Br	rt	0
$Pd(OAc)_2$	DMF	PPh_3	K_2CO_3	2 h	Br	100	37
$Pd_2(dba)_3$	DMF	dba	K_2CO_3	4 h	Br	100	16
$Pd_2(dba)_3$	Xylene[c]	$P(Furyl)_3$	Na_2CO_3	48h	Br	140	60
$Pd(PPh_3)_4$	Dioxane	$P(Ph)_3$	K_2CO_3	96 h	Br	100	32
$Pd(OAc)_2$	DMF	Cl^- [d]	K_2CO_3	12 h	Br	80	0
$Pd(OAc)_2$	Toluene	PPh_3	KOAc	48 h	Br	110	35
$Pd(OAc)_2$	Toluene	$P(OPh)_3$	K_2CO_3	48 h	Br	110	23
$Pd(OAc)_2$	Toluene	DPPE	K_2CO_3	72 h	Br	110	55
$Pd(OAc)_2$	Toluene	PPh_3	K_2CO_3	8 h[e]	Br	130	88
$Pd(OAc)_2$	Toluene	PPh_3	K_2CO_3	48 h	Br	110	69
$Pd(OAc)_2$	Toluene	PPh_3	K_2CO_3	36 h	I	110	74
$Ni(dppp)Cl_2$	Xylene[d]	DPPP	K_2CO_3	96 h	Br	120	0

a) All catalysts are used in 10 mole% with respect to **188**; b) Isolated yield of **189** starting from a reaction with 0.1 mmol **188**; c) A mixture of xylenes is used; d) Added as the tetrabutyl ammonium salt; e) Microwave irradiation. Irradiated at 150 W and 130 °C.

3.4.3. Properties

3.4.3.1. Crystallographic structure

As shown in Figure 4, the boron centre of **189** adopts a tetrahedral configuration with bond angles of ca. 110° and bond distances of 1.38 Å (B–

F) and 1.55–1.56 Å (B–N). In the BODIPY ring system, the two planar pyrrole subunits and the boron atom constitute a rigid plane, in which the maximum deviation of non-hydrogen atoms is 0.024 Å. The two fluorine atoms are equidistant above and under the mean plane of the BODIPY core, and the F-B-F plane is almost perpendicular (89.9°) to the plane of the ring system. The tolyl group at the *meso*-position makes an angle of 62.09° with the BODIPY plane, which is in the range of most BODIPY derivatives (40.3°–90°), but is smaller than the average value of 74.5° found in the CSD.[93] A remarkable structural feature is that all of the atoms in the benzofuran fragment also lie in the BODIPY plane, the deviation is within the 0.054–0.271 Å range. In addition, the 2-bromophenoxy substituent is inclined relative to the BODIPY plane, and the dihedral angle between both is 58.80°. For the doubly annulated dye **190**, similar observations can be made (Figure 4). For the BODIPY ring system the maximum deviation from planarity is 0.15 Å for the boron atom. The deviation from planarity for the boron atom, when considering the entire aromatic system is 0.19 Å. The tolyl group makes an angle of 55.4° with the BODIPY system.

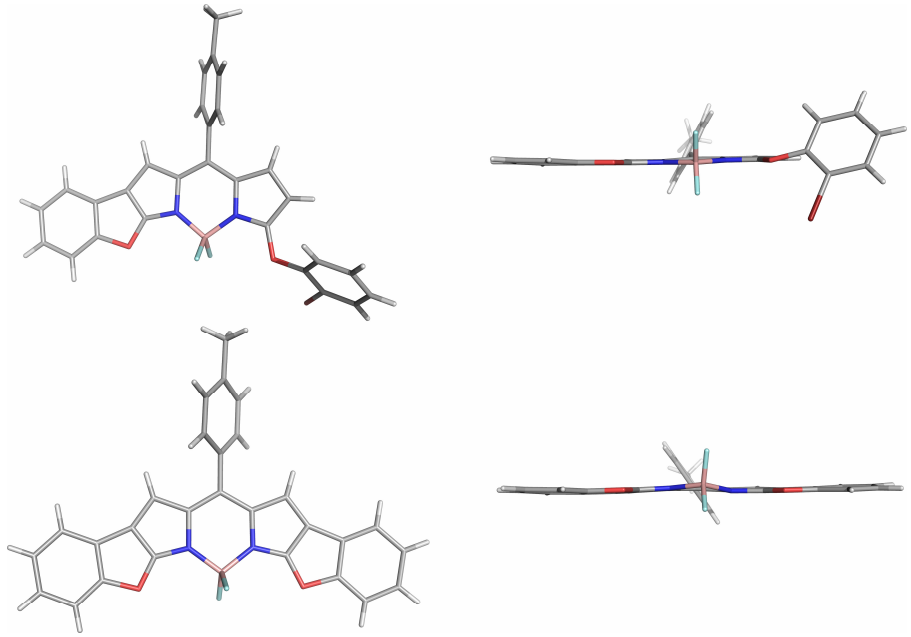


Figure 4: Stick representation of compound **189** (top) and compound **190** (bottom). To illustrate the planarity of the ring systems a bottom view is placed at the right. Created with PyMol, (DeLano, W.L. The PyMOL Molecular Graphics System (2002) on World Wide Web http://www.pymol.org).

93 The Cambridge Structural Database: a quarter of a million crystal structures and rising, F. H. Allen, *Acta Cryst. B*, **2002**, 58, 380.

3.4.3.2. Spectroscopic properties

Dyes **188-190** are strongly coloured solids with a metallic luster that form intensely coloured solutions with a bright fluorescence when irradiated (Figure 5).

Compound **188** displays the typical absorption features of classical BODIPY dyes in all solvents studied (Figure 5): that is, a narrow absorption band with a maximum in the 511–518 nm range, irrespective of the solvent employed. This absorption band is assigned to the $S_1 \leftarrow S_0$ transition, while an additional, considerably weaker, broad absorption band, observed at the short wavelength side, is attributed to the $S_2 \leftarrow S_0$ transition.

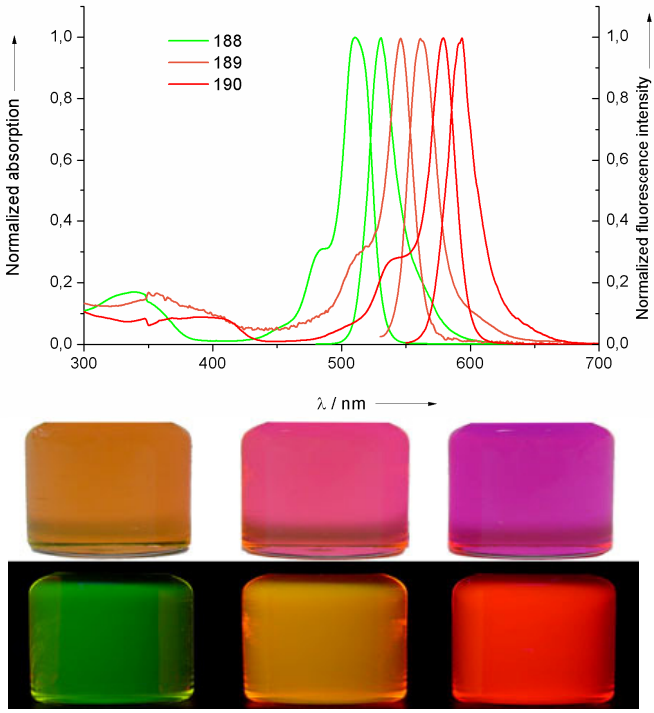


Figure 5: Normalized absorption (dash line) and fluorescence emission (solid line) spectra of **188** (blue), **189** (green) and **190** (red) in diethyl ether. Absorption (upper row) and fluorescence (lower row) emission colours of **188**, **189**, **190** (from left to right) in diethyl ether.

The main absorption band of **188** is hardly affected by solvent polarity: the maximum being slightly blue-shifted when the solvent is changed from toluene (518 nm) to acetonitrile or diethyl ether (511 nm), which is consistent with the general behaviour of BODIPY chromophores.

Derivative **188** also shows the typical emission features of BODIPY: i.e., a narrow, slightly Stokes-shifted band of mirror image shape, and fluorescence bands that are blue-shifted with decreasing solvent polarizability (from 537

nm in CCl_4 to 528 nm in methanol). The fluorescence quantum yields Φ_f are in the 0.27–0.71 range. Table 16 compiles the spectroscopic and photophysical data of **188** as a function of solvent.

The absorption and fluorescence emission spectra of **189** and **190** are of similar shape as those of similar, previously described difluoroboron dipyrromethene dyes.

Introduction of the benzofuran ring in **189** causes a large bathochromic (~30 nm) shift in both the absorption [λ_{abs}(max)] and emission [λ_{em}(max)] spectra compared to **188** (Table 17). The absorption and emission maxima of the most rigid structure **190** (with two benzofuran rings) are further red-shifted by approximately 30 nm compared with **189** (Table 18). The progressively more extended planarity of chromophore in the series **188**→ **189** → **190** accounts for the increasing bathochromic shifts of λ_{abs}(max) and λ_{em}(max). The fact that the absorption band positions of **188**, **189** and **190** do not show any particular trend as a function of solvent polarity suggests that the absorbing state of the dyes is weakly dipolar.

Table 16. Photophysical properties of **188** in several solvents. The solvents are listed according to increasing refractive index n.

Solvent	λ_{abs}(max) / nm [a]	λ_{em}(max) / nm [b]	$\Delta\overline{\nu}$ /cm^{-1} [c]	fwhm$_{abs}$ / cm^{-1} [d]	fwhm$_{em}$ / cm^{-1} [e]	Φ_f
methanol	512	528	592	726	926	0.41
acetonitrile	511	529	666	806	956	0.29
diethyl ether	511	530	702	992	848	0.38
acetone	512	530	663	766	919	0.29
ethyl acetate	513	531	661	724	990	0.27
2-propanol	514	531	623	721	848	0.58
butanenitrile	513	532	696	806	946	0.38
dibutyl ether	513	532	696	909	842	0.48
1-butanol	515	533	656	718	845	0.61
THF	515	532	620	757	979	0.29
1-pentanol	516	533	618	715	842	0.64
1,4-dioxane	515	534	691	754	839	0.47
CH_2Cl_2	516	533	618	754	876	0.44
cyclohexane	516	532	583	676	949	0.48
DMF	515	534	691	794	975	0.29
1-decanol	517	533	581	712	805	0.71
chloroform	518	535	613	710	833	0.63
CCl_4	518	537	683	671	833	0.58
DMSO	516	536	723	790	902	0.38
toluene	518	536	648	710	902	0.47

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift. d) Full width at half maximum of absorption. e) Full width at half maximum of emission.

Table 17. Photophysical properties of **189** in several solvents. The solvents are listed according to increasing refractive index n.

Solvent	λ_{abs}(max) / nm [a]	λ_{em}(max) / nm [b]	$\Delta\bar{\nu}$ /cm^{-1} [c]	fwhm$_{abs}$ / cm^{-1} [d]	fwhm$_{em}$ / cm^{-1} [e]	Φ_f
methanol	544	562	589	918	821	0.57
acetonitrile	544	563	620	954	785	0.59
diethyl ether	546	563	553	776	758	0.62
acetone	544	563	620	918	788	0.57
ethyl acetate	547	562	488	844	755	0.63
2-propanol	547	563	520	805	725	0.64
butanenitrile	544	564	652	990	845	0.70
dibutyl ether	549	565	516	733	722	0.57
1-butanol	549	565	516	802	722	0.56
THF	547	563	520	873	720	0.50
1-pentanol	549	565	516	800	750	0.71
1,4-dioxane	549	565	516	800	717	0.55
CH_2Cl_2	550	566	514	831	747	0.59
cyclohexane	551	564	418	661	662	0.69
DMF	547	567	645	1011	809	0.42
1-decanol	551	566	481	794	717	0.78
chloroform	553	567	446	791	682	0.58
CCl_4	553	567	446	656	714	0.63
DMSO	549	567	578	1003	742	0.53
toluene	553	569	508	788	742	0.48

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift. d) Full width at half maximum of absorption. e) Full width at half maximum of emission.

Light excitation yields fluorescence emission spectra with mirror image shape of the absorption spec tra. The Stokes shifts $\Delta\bar{\nu}$ are small for **188**, **189** and **190** and decrease with diminishing conformational mobility (651 ± 43 cm^{-1} for **188**, 533 ± 66 cm^{-1} for **187**, and 390 ± 52 cm^{-1} for **189**) (Table 16-20). The fluorescence excitation spectra of **188**, **189** and **190** match the absorption spectra in all cases and, moreover, λ_{ex}(max) = λ_{abs}(max). The observation that the emission band positions of **188-190** do not exhibit any distinct trend as a function of solvent polarity implies that emission occurs from the weakly dipolar, relaxed Franck-Condon excited state of the dyes.

Table 18. Photophysical properties of **190** in several solvents. The solvents are listed according to increasing refractive index n.

Solvent	λ_{abs}(max) / nm [a]	λ_{em}(max) / nm [b]	$\Delta\bar{\nu}$ /cm^{-1} [c]	fwhm$_{abs}$ / cm^{-1}	fwhm$_{em}$ / cm^{-1}	Φ_f
methanol	576	590	412	787	767	0.63
acetonitrile	578	592	409	876	767	0.58
diethyl ether	578	593	438	687	710	0.69
acetone	577	593	468	816	824	0.58
ethyl acetate	579	593	408	750	794	0.61
2-propanol	580	593	378	716	764	0.62
butanenitrile	579	593	408	842	875	0.64
dibutyl ether	582	594	3470	654	791	0.77
1-butanol	582	594	347	742	789	0.58
THF	580	595	435	745	786	0.56
1-pentanol	582	596	404	711	786	0.62
1,4-dioxane	583	596	374	768	768	0.62
CH_2Cl_2	583	597	402	740	807	0.63
cyclohexane	583	593	289	589	735	0.65
DMF	580	597	491	836	866	0.51
1-decanol	584	597	373	676	783	0.65
chloroform	586	599	370	732	805	0.63
CCl_4	588	598	284	641	754	0.59
DMSO	587	599	341	1346	890	0.75
toluene	587	602	424	699	799	0.58

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift. d) Full width at half maximum of absorption. e) Full width at half maximum of emission.

The increasingly restricted bond rotation in the ring-fused systems **189** and **190** explains the noticeably higher quantum yields Φ_f of **190** ($\Phi_f \geq 0.5$ in all 20 solvents studied) and **189** ($\Phi_f \geq 0.5$ in 18 out of 20 solvents) compared to those of **188** ($\Phi_f \geq 0.5$ in 6 out of 20 solvents). The molar absorption coefficients ε_{max} of **188**, **189** and **190** at the absorption maximum λ_{abs}(max) were determined in a number of solvents. The ε_{max} values of **188** in toluene, ethyl acetate and methanol were found to be $(35 \pm 2) \times 10^3$ L mol^{-1} cm^{-1}, $(45 \pm 4) \times 10^3$ L mol^{-1} cm^{-1} and $(42 \pm 3) \times 10^3$ L mol^{-1} cm^{-1}, respectively. The ε_{max} values of **189** in toluene, ethyl acetate and methanol were found to be $(42 \pm 2) \times 10^3$ L mol^{-1} cm^{-1}, $(72 \pm 4) \times 10^3$ L mol^{-1} cm^{-1} and $(69 \pm 6) \times 10^3$ L mol^{-1} cm^{-1}, respectively. The ε_{max} values of **190** in toluene, ethyl acetate and methanol were determined to be $(155 \pm 4) \times 10^3$ L mol^{-1} cm^{-1}, $(126 \pm 7) \times 10^3$ L mol^{-1} cm^{-1}, and $(126 \pm 6) \times 10^3$ L mol^{-1} cm^{-1}, respectively.

The oscillator strength values f[94] of **188** in toluene, ethyl acetate and methanol were found to be 0.248, 0.226 and 0.307, respectively. The corresponding f values of **189** in toluene, ethyl acetate and methanol were determined to be 0.390, 0.359 and 0.362, respectively, while those for **190** were 0.802, 0.744 and 1.145 in toluene, ethyl acetate and methanol, respectively.

Progressive reduction of the flexibility of the chromophore is reflected by the considerably higher ε_{max}, f and Φ_f values. The brightness, defined as the product of the molar absorption coefficient $\varepsilon(\lambda)$ at the excitation wavelength λ and the fluorescence quantum yield [$\varepsilon(\lambda) \times \Phi_f$],[84] intensifies considerably by restricting the conformational flexibility. The maximum values of the brightness [i.e., for $\varepsilon(\lambda) = \varepsilon max$ at $\lambda_{abs}(max)$] for **188** in toluene, ethyl acetate and methanol are 16450 L mol^{-1} cm^{-1}, 12150 L mol^{-1} cm^{-1} and 17220 L mol^{-1} cm^{-1}, respectively. For **189** in toluene, ethyl acetate and methanol, these values are 20160 L mol^{-1} cm^{-1}, 45360 L mol^{-1} cm^{-1} and 39330 L mol^{-1} cm^{-1}, respectively. For **189** in toluene, ethyl acetate and methanol, the respective values are 89900 L mol^{-1} cm^{-1}, 76860 L mol^{-1} cm^{-1} and 79380 L mol^{-1} cm^{-1}.

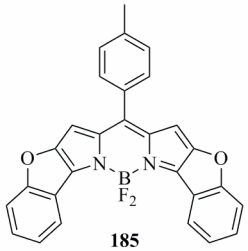
The absorption and emission spectral bandwidths of **188** to **190** are quite narrow [fwhmabs = $(7.6 \pm 0.8) \times 10^2$ cm^{-1} for **188**, $(8.4 \pm 1.0) \times 10^2$ cm^{-1} for **189** and $(7.7 \pm 1.5) \times 10^2$ cm^{-1} for **190**; $fwhm_{em} = (9 \pm 6) \times 10^2$ cm^{-1} for **188**, $(7.6 \pm 0.5) \times 10^2$ cm^{-1} for **189** and $(7.9 \pm 0.4) \times 10^2$ cm^{-1} for **190**]. Increasing the rigidity of the systems **189** and **190** – by benzofuran formation and by increasing the planarity of the chromophore – diminishes the degrees of vibrational freedom relative to **188**.

These spectral/photophysical properties can be compared to those of restricted BODIPY dyes published in the literature. The symmetric, constrained dye **185** (Scheme 76) of Burgess and co-workers with 2,6-dioxy benzofuran rings should be contrasted to compound **190** with 3,6-dioxy benzofuran rings. The most striking difference between these two dyes is the larger red shifts of $\lambda_{abs}(max)$ and $\lambda_{em}(max)$ for dye **185** which absorbs and emits light ~50 nm more to the red relative to dye **190**. This large difference reflects the improved conjugation of the 2,6-dioxy derivatives compared to the new 3,5-dioxy dyes. The benzo fused compound **187** also has bathochromically shifted $\lambda_{abs}(max)$ and $\lambda_{em}(max)$ relative to **190**. The Keio Fluor **186**, from Suzuki et al. with 2,6-dioxy furan rings as in **185**, (Scheme

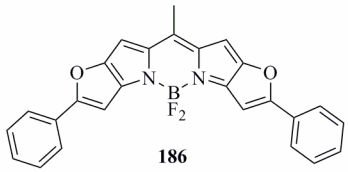
94 The oscillator strength f is directly related to the integral of the absorption band as follows: $$f = \frac{4.32 \times 10^{-9}}{n} \int \varepsilon(\bar{\nu}) d\bar{\nu}$$ where n is the solvent index of refraction and $\bar{\nu}$ is the wavenumber (in cm^{-1}).

76) have extremely high ε_{max} and Φ_f values. Conversely, the absorption and fluorescence emission maxima of **186** are located over 650 nm. Dye **186** can be regarded as a 3,5-distyryl substituted BODIPY (such as **102b**) with oxygen atom bridge linkers that preclude free rotation of the ethenyl fragments. The absence of a *meso*-substituent and hence limited conformational flexibility in **186** leads to very high quantum yields Φ_f. In order to understand all these experimental observations on ring-fused BODIPY compounds, we performed quantumchemical calculations, which are reported in the next section.

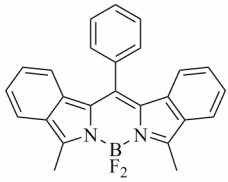
Table 19. Comparison of some spectral/photophysical properties of other rigid ring-fused BODIPY dyes



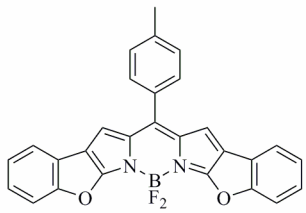
185



186



187



190

Product	λ_{abs}(max) / nm	λ_{em}(max) / nm	$\Delta\bar{\nu}$ /cm^{-1}	ε_{max} / L mol^{-1} cm^{-1}	Φ_f
190	586	599	370	155 000	0.63
185	637	647	243	151 000	0.34
187	600	609	246	-	0.99
186	652	661	209	314 000	0.90

3.4.3.3. Quantum chemical calculations

All dyes studied have a ring-fused BODIPY core. For all compounds investigated, ground-state geometry optimization was first performed at the semi-empirical AM1 level. These geometries were subsequently used as input for excited-state calculations at the AM1/SCI level (in the gas phase). The main goal of the theoretical work is to unravel the relationships between the nature and position of the substituents grafted on the BODIPY core and the resulting spectral properties, namely excitation energy and optical absorption cross-section.

To understand the effect of conformational constraints on the optical properties of BODIPY dyes, we performed calculations on molecules **188-190** (Table 20). Starting from **188**, the rigidity of the structure has been increased by the introduction of benzofuran rings instead of bromophenoxy groups. The results of the AM1/SCI calculations are presented in Table 20.

Table 20. Comparison of calculated and experimental photophysical properties of restricted BODIPY dyes. Calculated (AM1/SCI) (left) and measured (right) photophysical properties of compounds **188-190**, **185** and **186**.

	Theoretical values			Experimental values		
	transition energy / eV	transition wavelength / nm	f[d]	transition energy / eV	transition wavelength / nm	f[d]
188	2.382	521	0.7515	2.396[a]	518[a]	0.248[a]
189	2.303	538	0.8525	2.245[a]	553[a]	0.390[a]
190	2.206	562	1.0182	2.114[a]	587[a]	0.802[a]
185	2.069	599	0.7912	1.949[b]	637[b]	-
186	2.023	613	1.2316	1.904[b]	652[b]	-

a) Data in toluene. b) Data in chloroform. c) Data in cyclohexane. d) oscillator strength.

The increase in rigidity leads to a bathochromic shift of λ_{abs}(max): there is a red shift of ~18 nm (~0.08 eV) when one bromophenoxy group is replaced by a benzofuran ring (in **189**). When a second benzofuran ring is introduced (in **190**), the bathochromic shift reaches ~24 nm (~0.10 eV) in comparison to **189**. The calculations reproduce well the observed spectral shifts, even though the AM1/SCI values are systematically underestimated.
The experimental oscillator strengths, f, are in line with our theoretical findings: the oscillator strength f increases when the 3,5-substituents are frozen in a more rigid structure, as a result of the extended π-delocalization.
Differences between the frontier orbitals of the three compounds are only noticeable in the case of the HOMO: for **188**, the HOMO has no weight on the substituents (bromophenoxy rings). When replacing the bromophenoxy groups of **188** by either one or two benzofuran rings in **189** and **190**, respectively, the HOMO shows significant contributions on the substituent moiety thereby explaining the predicted and measured bathochromic and hyperchromic shifts.

It is instructive to compare **185** and **190** as these only differ by the position of the benzofuran rings on the BODIPY core: **188** presents 3,5-dioxy benzofuran rings whereas **185** features 2,6-dioxy benzofuran rings (see Scheme 76).

Experimentally, it has been found that **185** was more red-shifted than **190**, reflecting its improved conjugation. The theoretical results confirm this observation (Table 20).

Looking at the transition wavelengths (Table 20), we find λ_{abs}(max) = 562 nm for **190**, which is ~24 nm less than the experimental result. In the case of **185**, we find a larger difference with a transition at 599 nm, approximately 38 nm less than the experimental one. Again, although the theoretical values of the absorption maxima and of the spectral shifts are underestimated for both compounds, the qualitative trend is nicely reproduced by the calculations, with **185** showing a calculated bathochromic shift of ~37 nm (~0.14 eV) compared to **190** (against the experimental value of ~50 nm).

When comparing the frontier orbitals, a major visible difference can be noticed for the LUMO: in **190**, the LUMO has a vanishingly small weight on the benzofuran rings, while these contribute significantly to the LUMO wavefunction in **185**. This is confirmed by the computed transition densities (that provide a local map for the transition dipole and the excited-state localization) for the lowest electronic excitation (Figure 6). The transition is almost completely localized on the BODIPY core in **190**, yet one can see small but non- negligible contributions on the benzofuran rings in **185**, consistent with the extended conjugation. In a simple valence bond picture, the phenyl units in **190** are connected to the central pyrrole rings of the BODIPY core in the 'β' positions, while they are grafted in the 'α' positions for **185**, thereby explaining the more efficient delocalization in **185**.

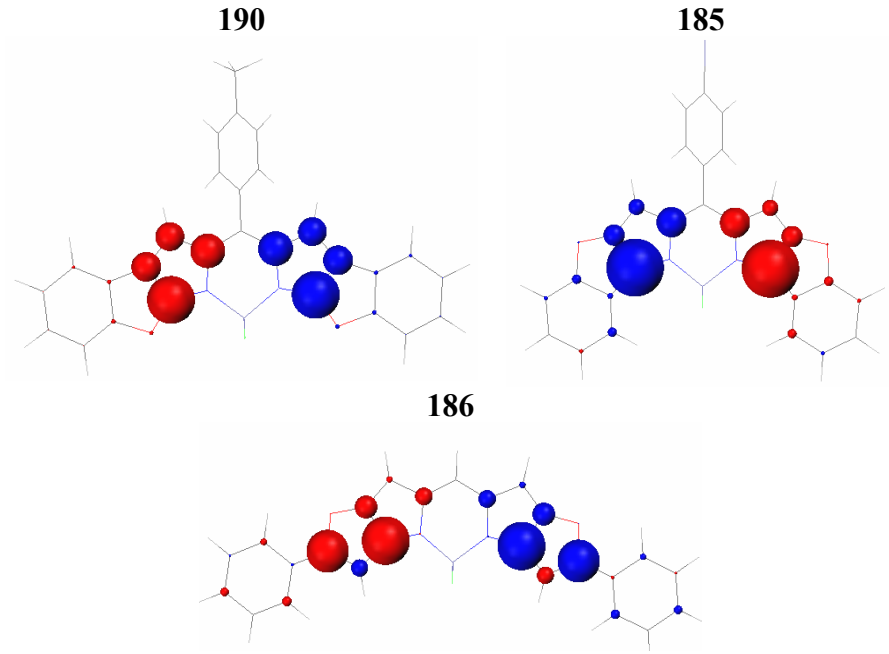


Figure 6. Transition densities of compounds **185**, **186** and **190**

3.4.4. Attempts to prepare sulfur- and nitrogen-containing analogues

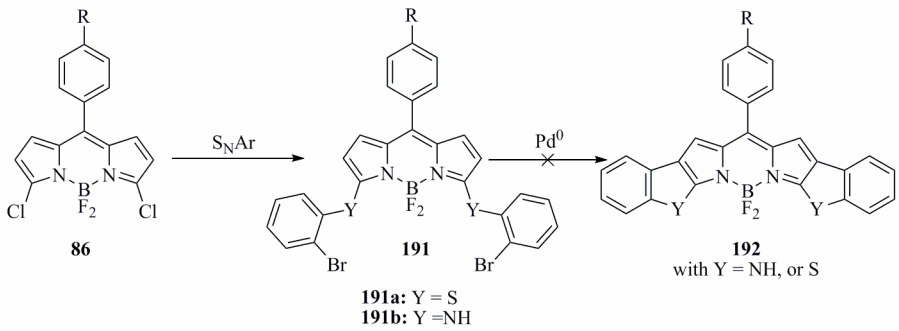
3.4.4.1. Placing the halogen on the aryl nucleophile

Using similar protocols, it was envisioned that the substitution products of *o*-brominated thiophenol and aniline should also furnish the corresponding benzothiophene and indole fused products (Scheme 79). These products are of particular interest, as the starting materials are already bathochromically shifted in both absorption and emission. Should the ring formation introduce comparable shifts, both restricted dyes would absorb and emit in the near infrared.

The synthesis of the starting materials **191** was reasonably straightforward, with high yields in the thiophenol case. On the contrary, double substitution with *o*-bromoaniline was particularly difficult and low yielding. This low yield can be attributed both to the lowered nucleophilicity of *o*-bromoaniline and the instability of the compound on silica, rendering isolation difficult, and the ring annelation was attempted with crude mixtures.

However, all attempts until now to effect the palladium catalyzed heterocycle formation failed. In the case of thioether **191a**, no reaction is observed. Possibly, the palladium catalyst is not able to enter a catalytic cycle due to strong complexation with the sulphur atoms.

For the nitrogen analogue **191b**, fast reaction was observed under the conditions optimized for *bis*-ether **188**. However, several side products were formed, and this, combined with the small amounts of product available, precluded isolation of the indole annelated product **192b** up to now.

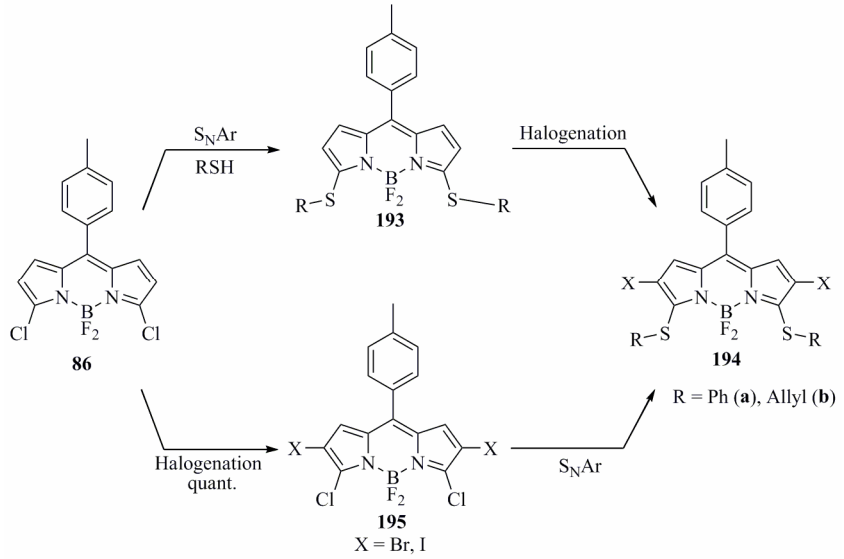


Scheme 79. Attempted ring formations towards the sulfur and nitrogen analogue

3.4.4.2. Placing the halogen on the BODIPY system

Faced with the problems in forming the other analogues, systems with a reversed reactivity were designed. Unlike the previously mentioned molecules, the halogen substituent needed for cyclisation would be located

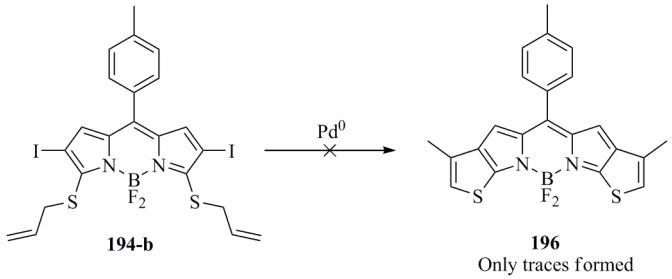
on the BODIPY itself. Again, two options are possible, halogenation before nucleophilic substitution or after the introduction of the nucleophile.
Substitution of 3,5-dichloro-BODIPY **86** with sulphur nucleophiles is fast and proceeds in quantitative yield.[48] Halogenation of these thioethers **193** with bromine or iodine monochloride is particularly rapid, but could only be effected in moderate yield. The second route, involving halogenation of 3,5-dichloro-dyes **86** is more promising. Halogenations with NBS or NBS/AIBN were slow and required large excess of reagents. However, the tetrahalogenated products **195** can be isolated in quantitative yield, using bromine and iodine monochloride in dichloromethane as halogenating agent. With an even decreased electron density, these systems are highly susceptible to nucleophilic attack. Thus, phenylsulfanylated and allylsulfanylated dyes **194** were obtained in near quantitative yield from substitution in basic acetonitrile.



86 **193** **194** **195**

Scheme 80. Routes to 2,6-dihalogenated-3,5-substituted dyes

Similar problems as with the previously mentioned dyes, were encountered during attempts to close such 2,6-halogenated systems. Despite prolonged reaction times, no formation of the conjugated products could be observed in the case of thiophenol adducts **194a**. Nevertheless, for the *bis*-(thioallyl)-ether **194b**, reaction to thiophene annelated BODIPY **196** did proceed, as observed by mass spectral analysis. The product was formed in a complex mixture, and optimized conditions for its isolation in substantial yield have not yet been found.



Scheme 81. Palladium catalyzed cyclisation route to *bis* thiophene **196**

3.4.5. Conclusions

We have demonstrated that the combination of nucleophilic aromatic substitution of 3,5-dichloro-4,4-difluoro-8-(4-tolyl)-4-bora-3a,4a-diaza-s-indacene with *o*-bromophenol followed by palladium catalyzed benzofuran ring formation is a powerful and facile method for the formation of BODIPY dyes with bathochromically shifted visible absorption and fluorescence spectra with considerably higher ε(λ), f and Φ_f values. The described dyes **188** to **190** have increasingly restricted conformational mobility. Their UV-vis absorption and fluorescence emission spectra have been determined as a function of solvent. These BODIPY derivatives show small Stokes shifts and narrow absorption and emission bands. The small solvent-dependent shifts of the absorption and emission bands of **188-190** are primarily determined by solvent polarizability. The absorption and emission maxima of **189** are shifted to the red by ~30 nm in comparison to the unconstrained structure **188**. The most rigid structure **190** displays an additional bathochromic shift in both the absorption and emission spectra of ~30 nm compared to **189**. These results are also supported by the quantum chemical calculations which showed that the increase of conformational constraints leads to larger bathochromic shifts. The crystal structures of the three dyes have been determined and show an increasing planarity of the chromophore in line with a reduction of the conformational flexibility.
All efforts to extend this reactivity to nitrogen and sulphur analogues failed, and several other strategies were equally unsuccessful. However, several other ring closure strategies remain to be tested or optimized.

3.5. Oxidative substitution on BODIPY dyes

3.5.1. Oxidative nucleophilic substitution of hydrogen on BODIPY dyes

The recent interest in direct functionalization rather than by functional group interconversion has opened up a rapidly expanding field of chemistry.[63] Several approaches have been developed to introduce functional groups, especially on aromatic systems and through transition metal catalysis. As these methods alleviate the need for tedious introduction of substituents and greatly improve synthetic power, this approach will become increasingly important.

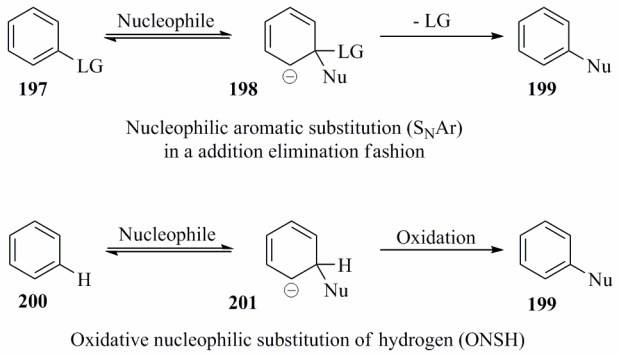
Application of such procedures to the popular boron dipyrromethene (BODIPY) fluorophores is limited to palladium and iridium catalyzed double bond introduction at the 2,6-positions.[64,65] Up to now, no selective direct substitution of hydrogen at the spectroscopically interesting 3,5-positions has been reported. For derivatization of BODIPY dyes at these positions, chlorinated derivatives have recently been shown to be highly versatile.[46,89]

The ease of introduction of nucleophiles via nucleophilic aromatic substitution (S_NAr) has been exploited in the synthesis, and subsequent functionalization, of several halogenated BODIPY dyes.[49,50,51]

In the addition/elimination mechanism for S_NAr, addition of a nucleophile at the *ipso* position of an electron withdrawing leaving group breaks the aromaticity and results in intermediate **198** (Scheme 82). Elimination of the leaving group restores aromaticity and yields the substituted product **199**.

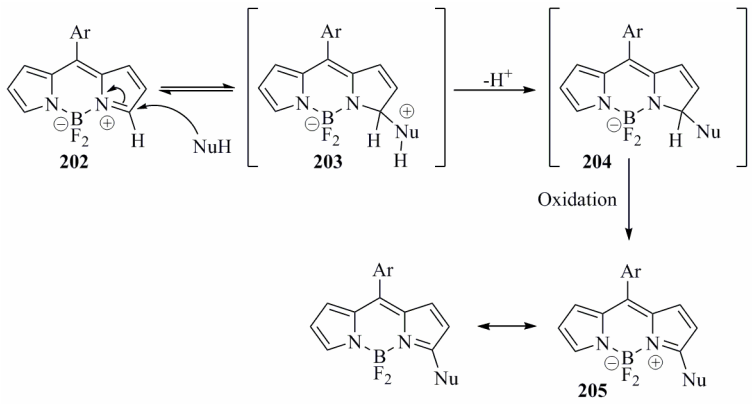
In contrast with S_NAr, the oxidative nucleophilic substitution of hydrogen (ONSH) is less well-known.[95] Generally, electron poor aromatic systems are susceptible to equilibrated nucleophilic attack at activated positions, forming a σ_H-adduct **201**. Hydride does not act as a leaving group from this adduct, but an oxidation step can be used to re-establish aromaticity.

95 M. Mąkosza and K. Wojciechowski, *Chem. Rev.*, **2004**, 104, 2631.



Scheme 82. Mechanistic comparison of S_NAr and ONSH

We reasoned that the electron poor 3,5-positions of BODIPY dyes **202** could undergo this ONSH at the most electrophilic azine-like 3-carbon (Scheme 83). The resulting negative charge on the σ_H-adduct **203** would be stabilized by the boron complex, and oxidation of the negatively charged intermediate **204** could result in the substitution product **205**.



Scheme 83. Oxidative nucleophilic substitution of hydrogen on BODIPY dyes

Much to our delight we indeed observed reaction upon stirring a *meso*-phenyl model BODIPY **202**, in butylamine as the solvent, under air. The yield was rather low, and from an optimization of the reaction procedure (Table 21), it was clear that the reaction proceeded preferably in polar solvents. As for the oxidizing agent, DDQ, CAN or silver permanganate[96] were able to effect the reaction, but superior yields of **205a** were obtained under oxygen atmosphere in DMF.

96 A. Soldatenkov, A. Temesgen, N. Kolyadina, *Chem. Heterocycl. Comp*., **2004**, 40, 537.

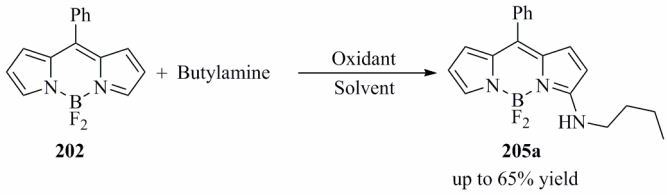


Table 21. Optimization of oxidative nucleophilic hydrogen substitution with butylamine.

Solvent	Oxidizer	Reaction Time	Yield (%)
-[a]	Air	16h	11
CH_3CN	O_2	5 days	33
THF	O_2	14 days	16[b]
DMSO	O_2	24h	41
DMF	**O_2**	**16h**	**65**
NMP	O_2	16h	55
DMF	Air	24h	48
DMF	DDQ	48h	26
DMF	PCA	48h	31
DMF	$AgPyMnO_4$	48h	16

a) butylamine was used as the solvent; b) Reaction not complete at this stage

Amine nucleophiles were highly reactive under the given conditions, and both primary (Table 22, entry 1,2 and 5) and secondary amines (entry 3 and 4) readily participated in the ONSH reactions. Due to the strong deactivation of the remaining α-position caused by the amine substituent, no disubstituted product was formed. Aniline failed to substitute the model compounds under the given conditions, and this presumably because of its lowered nucleophilicity.

Carbon nucleophiles showed excellent reactivity. Indeed, dimethyl malonate addition resulted in the desired substituted ester in good yield (entry 7), and this under mildly basic conditions. By increasing the amount of malonate and the reaction time the reaction goes to disubstitution in excellent yield (entry 9). Attesting to the generality of the reaction was the rapid and clean incorporation of nucleophiles such as enolates of ketones and esters. All the substitutions proceed at room temperature, both for amine and carbon nucleophiles. Heating only led to decreased yields.

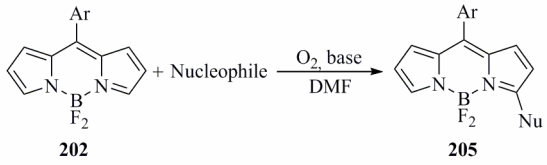


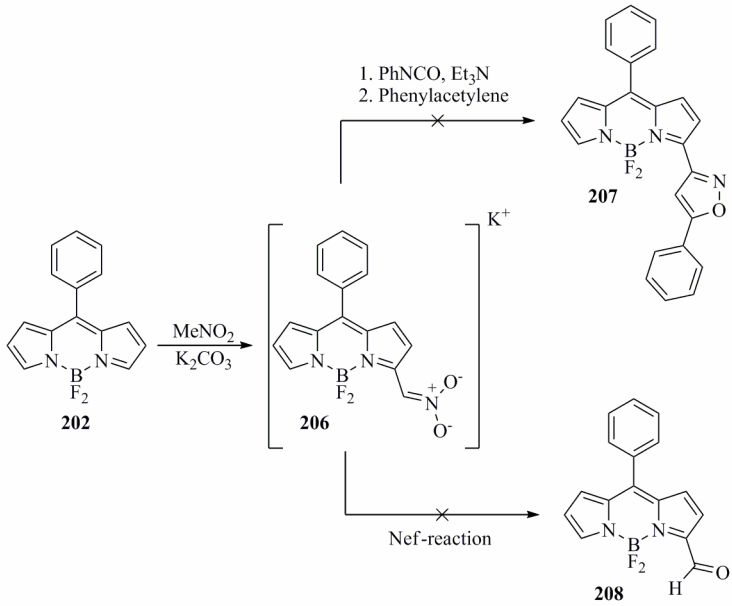
Table 22. Scope of the ONSH of α-unsubstituted BODIPY dyes

Entry	Nucleophile	Base[a]	reaction time	Product	yield[b] (%)
1	$BuNH_2$	-	16h	**205a**	65
2	$DodecylNH_2$	-	16h	**205b**	75
3	Piperidine	-	16h	**205c**	68
4	Morpholine	-	24h	**205d**	64
5	$BnNH_2$	-	16 h	**205e**	85
6	Aniline	-	7 days	-	-
7	$(MeOOC)_2CH_2$	K_2CO_3	20 h	**205f**	70
8	$(t\text{-}BuOOC)_2CH_2$	K_2CO_3	36 h	**205g**	72
9	$(t\text{-}BuOOC)_2CH_2$[c]	K_2CO_3	20 h	**205h**	80
10	$PhCOCH_3$	KO*t*Bu	6 h	**205i**	59
11	$EtOOCCH_2Ph$	KHMDS	6 h	**205j**	63
12	BuSH	K_2CO_3	6 days	-	~10[d]
13	PhSH	K_2CO_3	6 days	-	~10[d]
14	BuOH	NaH	6 days	-	-
15	PhOH	K_2CO_3	6 days	-	-

a) For amines, a second equivalent of amine is added; b) Isolated yields for reactions at 0.5 mmol scale; c) Product of double substitution, at both the 3- and 5-position; d) Isolated as an inseparable mixture of starting material, monosubstituted and disubstituted product.

The addition of nitromethane is very fast. However, the product formed could not be isolated. Combining the electron poor BODIPY with the nitro group renders the remaining hydrogens strongly acidic, and the compound is always present as, presumably, the nitronate **206**. Purification over silica fails for this reason. Attempts to use the crude product in the Nef reaction to aldehyde **208**, were unsuccessful or resulted in complex reaction mixtures, both under standard conditions[97] or DBU[98] and oxone[99] mediated. However, in the nitronate based 1,3-dipolar cycloaddition to isoxazole **207** traces of the isoxazole product were observed, so this reaction remains to be optimized.

97 J. Nef, *Liebigs Ann. Chem.*, **1894**, 280.
98 R. Ballini, G. Bosica, D. Fiorini, M. Petrini, *Tetrahedron Lett.*, **2002**, 43, 5233.
99 P. Ceccherelli, M. Curini, M. C. Marcotullio, F. Epifano, O. Rosati, *Synth. Commun.*, **1998**, 28, 3057.



Scheme 84. Attempted derivatisation of nitromethane adduct **204**

Conversely, oxygen and sulphur centred nucleophiles did not lead to the formation of products. In the case of the oxygen nucleophiles butoxide or phenoxide, formation of substitution products could not be observed. Substitution with sulphur nucleophiles, such as butanethiol or thiophenol, was very slow and resulted in inseparable mixtures of mono and disubstituted products. Prolonged reaction periods with excess of sulphur nucleophiles only led to disappearance of the thiol via oxidative disulfide formation.

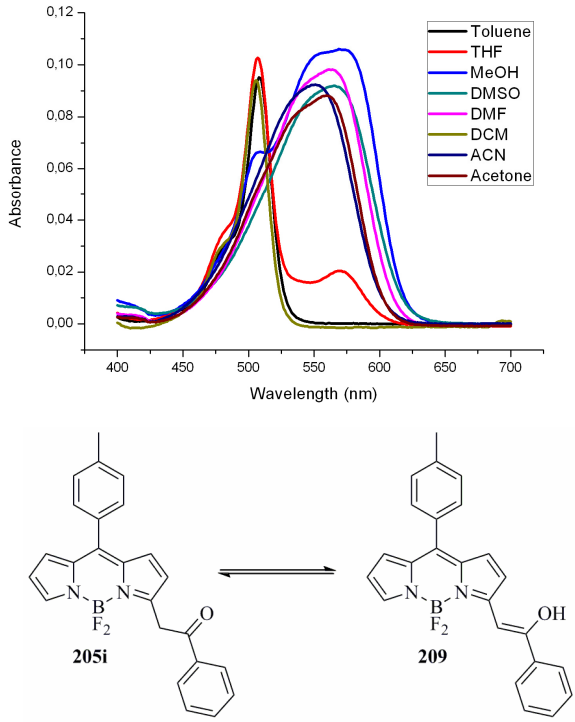
This low reactivity can be rationalized via the nucleophilic addition equilibrium (Scheme 83). In the case of thiolate and alkoxide, the σ_H-adduct **203** does not exist long enough to be efficiently oxidized. In the case of amine nucleophiles, removal of the proton from the σ_H-adduct **203** produces a stable intermediate **204** that can only decompose by releasing a poor amide leaving group, and thus the equilibrium is pushed towards the oxidation product. Similar considerations can be made for the carbon nucleophile adducts.

For carbon nucleophiles, products formed are present in the reaction mixture as their corresponding stabilized enolates, and a strong colour change from purple to orange can be observed upon acidification of the mixtures after completion of the reaction.

The existence of this enolate was proven by an NMR study of dye **205i**. Under neutral, apolar conditions, this compound is present as the keto form. But, upon addition of a base, the concomitant colour switch could be related to a disappearance of the carbonyl function and the appearance of a new

double bond in **209**. The process is fully reversible, and after addition of acid, the keto form **205i** was again the sole product.

Figure 7. Solvent polarity dependence of the acetophenone product



This equilibrium can also be visualized by the solvent dependency of the absorption. In an apolar solvent, like toluene or dichloromethane, the compound displays typical BODIPY absorbance around 510 nm. However, upon increasing the polarity of the solvent, a dramatic red shift takes place, giving an exceptionally large bathochromic shift of up to 100 nm in methanol. An intermediate situation can be observed for THF, where most of the compound is in the keto form, with a shoulder of the enol form around 570 nm. Similar to the NMR-experiments, the gradual addition of base to the compound in THF induces a shift to the enol form. All compounds have rather low quantum yields, attributed to free rotation of the *meso*-aryl substituent. The general photophysical studies of nitrogen and carbon substituted BODIPY dyes have been reported previously.

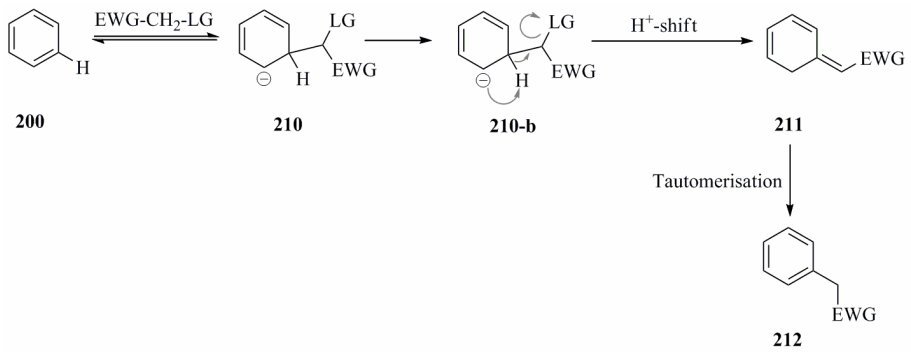
Table 23. Spectroscopic data of products originating from ONSH on BODIPY dyes

BODIPY	Solvent	λ_{abs} [a] / nm	λ_{em} [b] /nm	$\Delta\bar{\nu}$ [c] /cm^{-1}	Φ_f
205a	MeCN	466	530	2591	0.013
	MeOH	468	529	2464	0.012
	THF	493	533	1522	0.019
	Toluene	505	533	1040	0.033
205f	MeCN	502	520	690	0.017
	MeOH	503	520	650	0.041
	THF	506	523	642	0.064
	Toluene	509	526	635	0.14
205h	MeCN	503	521	687	0.03
	MeOH	504	520	611	0.040
	THF	507	523	603	0.06
	Toluene	509	527	671	0.14
205i	MeCN	551	592	1257	0.002
	MeOH	569	625	1575	0.022
	THF	506	523	642	0.08
	Toluene	508	526	674	0.087

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift.

3.5.2. Vicarious nucleophilic substitution on BODIPY dyes

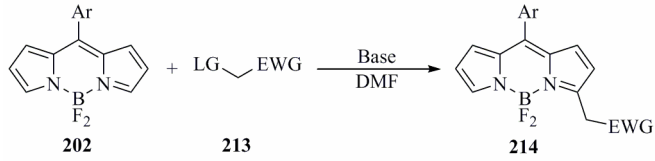
After the initial success of the oxidative nucleophilic hydrogen substitution on BODIPY, attempts were made to carry out vicarious nucleophilic substitution. In this mechanism, placement of a leaving group on the nucleophile favours a base catalyzed elimination/rearomatization from intermediate **210**.



Scheme 85. Mechanism of the vicarious nucleophilic substitution of hydrogen

The first experiments were not successful, with starting material as the only product recovered from the mixtures. However, the discovery that only strong base could effect the elimination rapidly led to an optimized procedure. The vicarious substitution allows effective introduction of acetic acid derivatives, with chloride and bromide acting as efficient leaving groups in the reaction. Moreover, also thiophenol acts as leaving group, and after only a few minutes of stirring the mixture in DMF with base, all the starting material is consumed to yield ester substituted dye **214**. Further work is needed to asses the full scope of this vicarious nucleophilic hydrogen substitution.

Scheme 86. Vicarious nucleophilic hydrogen substitution on BODIPY



202 **213** **214**

Table 24. Results from vicarious nucleophilic hydrogen substitution

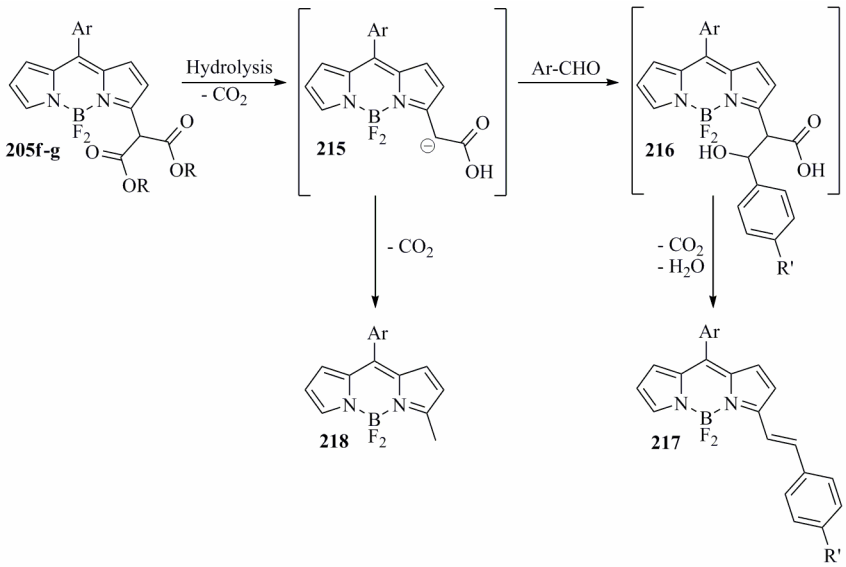
Product	LG	EWG	Base	Yield
214a	Br	COOMe	KO*t*Bu	67
214a	Br	COOMe	DBU	66
214b	Br	COO*t*Bu	KO*t*Bu	87
214a	Cl	COOMe	KO*t*Bu	42
214b	SPh	COOtBu	DBU	86

3.5.3. Attempted application to olefination reactions

3.5.3.1. Doebner modification of Knoevenagel like reactions

The application of the acidity of the 1,3,5,7-methyl substituents has been used extensively for the attachment of functionalities. These groups react in a base mediated condensation, comparable with the aldol condensation, although in the field of BODIPY chemistry, it is often referred to as a Knoevenagel condensation.
Despite its widespread use, general optimized conditions have not yet been found and yields usually lie in the range of 20-30%. It was reasoned by us, that one could change from the aldol type reaction to the Doebner modification of the Knoevenagel condensation. For this purpose, enolizable carboxylic acids had to be placed at the 3,5-positions. Addition of the enolate followed by concerted elimination should then yield the styrene derivatives.

Oxidative addition of malonates efficiently provided both the single and disubstituted products (**205f-h)**. All attempts to get these compounds to undergo one-pot Doebner reactions (Scheme 87), both under acidic, basic and neutral conditions failed. The desired compounds **217** were formed only in yields up to 10%, and despite extensive efforts, no optimized conditions could be found. The styrylated products were contaminated with substantial amounts of the formally methylated products **218**, which are the result of double decarboxylation. Performing the same reaction with *bis* malonate **205h** does result in the *bis*-styrene, but the compound is accompanied by all possible decarboxylation products, and is therefore extremely difficult to purify from the complex mixture.



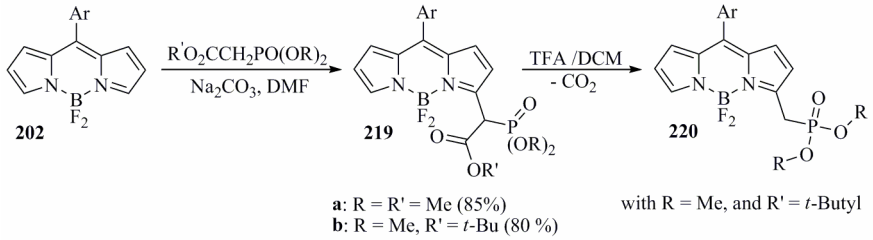
Scheme 87. Doebner condensation of BODIPY malonates and side product arising from double decarboxylation

When the vicarious hydrogen substitution started to deliver results, and the carboxylic esters **214** became available on large scale, some tests were performed to use these products in the condensation reactions. Regretfully, decarboxylation was again competing with condensation, and so far, no satisfying conditions have emerged.

3.5.3.2. Horner-Wadsworth-Emmons olefination

However, this facile decarboxylation on the α-carbonatom led to other routes to carbon-carbon double bonds. Both as an alternative to the failing Doebner reaction, and as proof-of-concept for the decarboxylative functional group introduction, BODIPY dyes with appending phosphonoacetates **219** were prepared. The oxidative substitution is particularly effective, and was carried out in large scale.

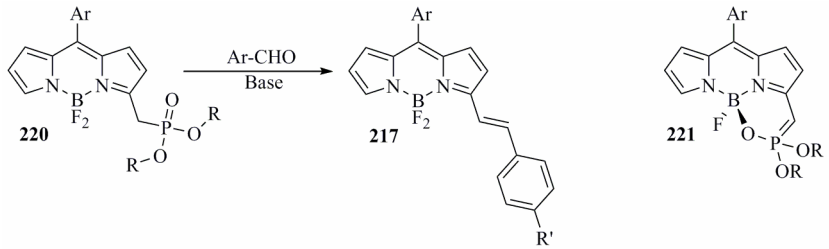
As the subsequent hydrolysis of the methyl ester **219a** was low yielding, we opted for the *tert*-butyl ester **219b**. This ester was cleaved and decarboxylated in one step and quantitive yield to **220** using diluted trifluoroacetic acid in refluxing dichloromethane. All the compounds were prepared with *meso*-phenyl and *meso*-2,6-dichlorophenyl substituents, as the latter has a higher quantum yield of fluorescence due to the restricted rotation.



Scheme 88. ONSH with phosphono acetates followed by hydrolysis of the ester and decarboxylation leads to BODIPY phosphonates

The actual Horner reaction however, could only be effected in low yields (Scheme 89), with yields of styrylated dyes **217** again not rising above 10%. From mass-spectrometric examination of the reaction mixtures, it appears that the stabilized phosphono enolate substitutes a fluorine on the boron, leading to closed product **221**, however, this product has not been isolated successfully.

As this process would be highly dependent on counter ion and solvent, numerous conditions were tested, but without success so far.



Scheme 89. Attempted Horner-Wadsworth-Emmons olefination and proposed major side product formed

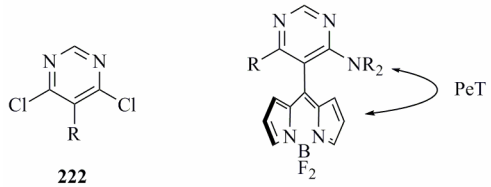
3.5.4. Conclusion

In conclusion, α-unsubstituted BODIPY fluorophores are shown to be highly reactive towards the oxidative nucleophilic substitution of the α-hydrogen atom, introducing functionality in a single step. The novel methods of ONSH and VNS are an excellent alternative to the previously reported halogenated systems, and conveniently use cheap and widely available chemicals. The full scope of these reactions remains to be determined, but hopefully these procedures will allow fast and versatile labelling, as well as tackle some of the old problems of BODIPY chemistry.

3.6. *meso*-Dichloropyrimidinyl BODIPY's

3.6.1. Introduction

All the reactive systems described in chapters 3.1 to 3.5 introduce functionality directly onto the BODIPY core. Therefore, they strongly interact with the fluorescent properties of the dyes. Although this is often desirable, it might also be of use to have a versatile linkage unit that would allow similar chemistry with retention of the original spectroscopic properties.
The 4,6-dichloropyrimidinyl moiety **222** has been extensively used in the preparation of functional supramolecular systems such as porphyrins, corroles and calixarenes, where it has proven a versatile partner for functionalization.[100] Accordingly, BODIPY dyes with such appending groups should be interesting dyes for labelling purposes.
On the other hand, in such systems, the introduced groups would be located above and below the plane of the fluorescent dye, and could therefore still have a *through space* effect on the photophysical properties. For example, it has been shown in the synthesis of maleimide sensor **47** that the 2'-position is the ideal location for ON-OFF sensing behaviour based on nitrogen substituents.[23]



Scheme 90. Structure of 2,4-dichloropyrimide and ratio of design.

3.6.2. Synthesis

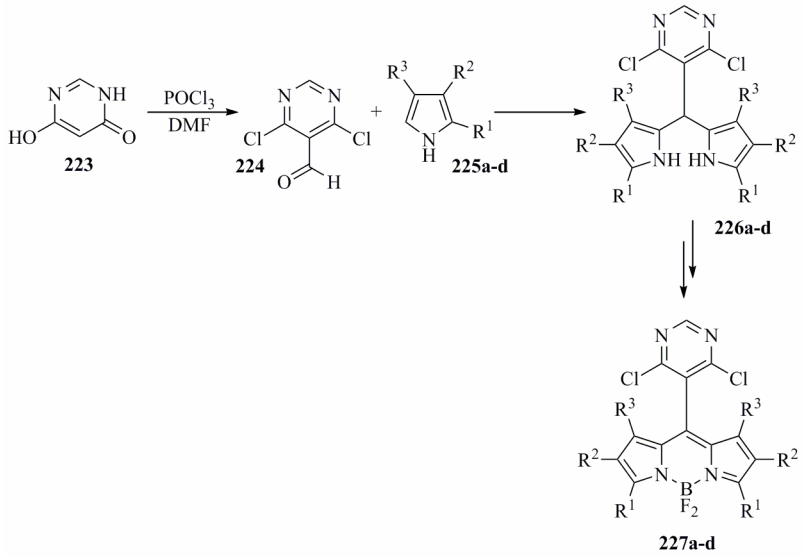
3.6.2.1. Synthesis of model systems

Meso-(4,6-dichloropyrimidin-5-yl)-BODIPY compounds were conveniently prepared according to established procedures. Starting from commercially available 6-hydroxypyrimidin-4-one **223** we were able to obtain the dichlorinated pyrimidine carbaldehyde **224** in good yield according to a previously published procedure.[101] An acid catalyzed condensation of this

100 W. Maes, W. Dehaen, *Pol. J. Chem.*, **2008**, *82*, 1145.
101 A. Gomtsyan, S. Didomenico, C. Lee, M. Matulenko, K. Kim, E. Kowaluk, C. Wismer, J. Mikusa, H. Yu, K. Kohlhaas, M. Jarvis, S. Bhagwat, *J. Med. Chem.*,

aldehyde with several selected pyrroles **225a-d** yielded the dipyrromethanes **226a-d**. The unsubstituted dipyrromethane **226a** can be prepared through a previously reported method. This method employs only 3 equivalents of pyrrole and water as the solvent, in contrast to the standard procedure, where pyrrole is the solvent. In the case of an α–substituted pyrrole, polycondensation is no issue, and the commercially available 3,5-dimethylpyrrole, **225b**, can undergo the condensation with trifluoroacetic acid (TFA) catalysis in dichloromethane. The other α–substituted pyrroles, **225c** and **225d**, can be obtained from a Trofimov reaction,[102] furnishing the pyrroles in a single step with moderate yields and the possibility for large scale reactions.[103]

These dipyrromethanes **226a-d** were then oxidized to the corresponding dipyrromethenes using DDQ. In a final step, the dipyrromethenes were complexed with boron trifluoride using triethylamine in dichloromethane. Atypically, the complexation of these dyes can take several days to reach completion. This entire sequence could also be performed in a one pot procedure with fair-to-excellent yields. The desired BODIPY dyes **227a-d** can then be purified by flash column chromatography and crystallization.



Scheme 91. Synthesis of 8-(4,6-dichloropyrimidin-5-yl)-BODIPY

2002, 45, 3639.

102 (a) E. Schmidt, A. Mikhaleva, A. Vasil'tsov, A. Zaitsev, N. Zorina, *ARKIVOC*, **2005**, 7, 11; (b) B. Trofimov, *Adv. Heterocycl. Chem.*, **1990**, 51, 177.

103 A detailed experimental procedure followed for large scale Trofimov reactions is described in the experimental section.

Table 25. Synthesis of 8-(4,6-dichloropyrimidin-5-yl)-BODIPY

Product	R^1	R^2	R^3	Yield (%)[a]
227a	H	H	H	22
227b	Me	H	Me	30
227c	Ph	H	H	80
227d	Dihydrobenzindole		H	48

a) Overall yield from **222**

3.6.2.2. Substitution of the dichloropyrimidines

Nucleophilic substitution

Initially, we applied this protocol to 2,4-dimethylpyrrole **225b**, resulting in the 1,3,5,7-tetramethyl substituted BODIPY **227b**. We subjected the latter to several nucleophiles under a wide range of conditions to test its reactivity in nucleophilic aromatic substitutions. However, no reaction could be observed. It was only after several hours in DMF at elevated temperatures that we were able to observe substitution by thiophenol. After disappearance of the starting material, only 15 % of the monosubstituted product could be recovered. This might be caused by steric hindrance by the 1,7 methyl groups which disfavours the transition state of the nucleophilic attack. To test this hypothesis, we decided to continue work on 1,7-unsubstituted compounds **227c-d**.

With the diphenyl dye **227c** as a model system, the substitution with several nucleophiles was tested and immediate incorporation of these nucleophiles with excellent yields could be observed (Table 26). Most reactions proceeded in superb yields and spectroscopically pure samples could be obtained after flash column chromatography or recrystallization. Substitutions with phenol were carried out in DMF with 18-crown-6 as a catalyst, to yield both the monosubstituted **228a** and disubstituted product **229a** Similar yields were obtained for the substitution with 2-naphthol to afford dye **229c**. The crown ether catalyst was not necessary for sulphur nucleophiles **228b**. Again, longer reaction times and more nucleophile lead to the disubstituted product **229c**. Nitrogen centred nucleophiles, such as aniline and piperidine, did not react under the conditions described here.
Aliphatic oxygen nucleophiles, methoxide and ethoxide, showed only limited reactivity, resulting in sluggish reactions where competition of fluorine substitution at boron becomes a problem. This fluorine substitution has been described in the literature, but did not occur in our case with phenolate anion.

We could also perform nonsymmetric substitutions by adding a second nucleophile after the completion of the first substitution, as can be monitored using thin layer chromatography. Thus, after complete substitution with phenol, addition of an equivalent of thiophenol or sodium thiomethoxide, results in nonsymmetric substituted dyes **229d** and **229e**.
Proceeding at room temperature, the developed method is very mild, but takes 16 to 60 hours. Gentle heating of the reaction mixtures speeds up the reaction and all the reactions were finished in a few hours. Heating to 100 °C also allows to obtain the disubstituted products within acceptable reaction times. It is noteworthy that the first substitution lowers the reactivity of the remaining chlorine significantly. In the presence of 1 equivalent of nucleophile only monosubstituted product was observed.

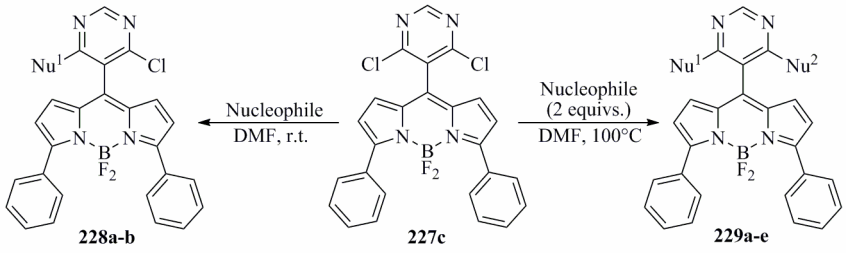
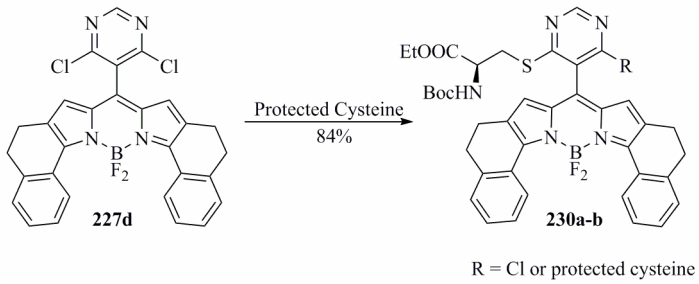


Table 26. Nucleophilic substitutions on 3,5-diphenyl-BODIPY **227c**.

Product	Nu^1	Nu^2	Conditions[a]	Time (h)	Yield[b]
228a	OPh	Cl	A	16	98
229a	OPh	OPh	A	60	85
228a	OPh	OPh	B	4	96
229b	ONapht[c]	ONapht[c]	B	4	75
228b	SPh	Cl	A	4	93
229c	SPh	SPh	A	40	91
229c	SPh	SPh	B	1	93
229d	OPh	SPh	B	1	80
229e	OPh	SMe	A	20	94

a) conditions: A: r.t. DMF; B: 100 °C, DMF. b) Isolated yields for a 0.2 mmol reaction; c) From 2-naphtol

The excellent yields for thiol substitution under mild conditions led us to try cysteine as nucleophile. For this purpose, the constrained *bis*-(dihydrobenzindole) dye **227d** was selected, as it emits light in the near infrared and is therefore an ideal probe for labelling of biomolecules.
Substitution with a protected cysteine derivative proceeded in excellent yield, and both the mono and disubstituted product (**230a-b**) could be obtained (Scheme 92).



Scheme 92. Nucleophilic aromatic substitution with a protected cysteine derivative

Palladium catalyzed reactions

Next, we turned our attention to palladium catalyzed coupling reactions. While trying to apply the Suzuki protocol under standard conditions we saw a very slow reaction. It was only after several hours at elevated temperatures that we began to observe coupling. To get the reaction to an acceptable speed, rather large amounts of catalyst had to be used. As microwave irradiation is known to speed up these reactions, we attempted microwave enhanced Suzuki reaction. Fortunately, we could isolate the desired product **231a** in excellent yields after only fifteen minutes of microwave irradiation at 130 °C. To reach the doubly arylated dye **231b**, it is sufficient to use two equivalents of the boronic acid.

Unlike the Suzuki reaction, the Stille reaction of our model system with tetraphenyltin proceeded at an acceptable rate with conventional heating, and either the mono or disubstituted model dye (**231a** or **231b**) were obtained at reflux in toluene.

The Sonogashira reaction was tested with phenylacetylene in refluxing THF with an amine base. After a few hours of reaction at 50 °C, we were able to isolate either the monosubstituted or the disubstituted product (**231c** or **231d)** in good yields. Again, there was good selectivity of the substrate for monosubstitution over disubstitution. Only small amounts of the disubstituted product could be observed as the synthesis of monosubstituted dye approached completion.

All attempts to apply Heck reaction to the substrate led to total decomposition of the chromophore.

Finally, we sought an alternative route to the much sought after amine substituted dyes, which are impossible to prepare using nucleophilic substitution. As Hartwig-Buchwald type palladium catalyzed aminations have rapidly become an established route to substituted amines, this reaction was tested. Although initial experiments with mild base such as tertiary butoxide or phosphate anion were unsuccessful, the switch to strong base with sterically demanding ligands allowed us to reach the aminated dye **231e**, in an acceptable yield and short reaction times.

Sadly, but not to our surprise, the *bis* aminated dye remained elusive due to the very strong deactivation due to the first substituent. Long reaction times under the active conditions only led to monosubsitution and subsequent decomposition.

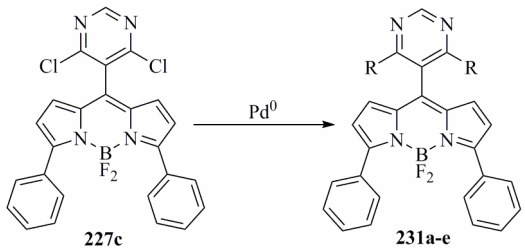


Table 27. Palladium catalyzed substitutions on 3,5-diphenyl-BODIPY **227c**.

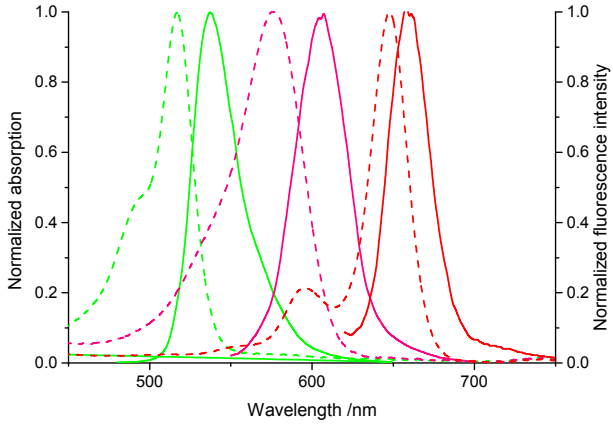
Product	R^1	R^2	Conditions	Time	Yield (%)
231a	Ph	Cl	A	72h	22
231a	Ph	Cl	B	15 min.	63
231b	Ph[b]	Ph	B	15 min.	89
231a	Ph	Cl	C	16h	72
231b	Ph	Ph	C	24h	64
231c	C≡CPh	Cl	D	16h	69
231d	C≡CPh	C≡CPh	D	24h	56
231e	*N*-Piperidine	Cl	E	1h	52

a) A: Conventional Suzuki reaction: $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux; B: Microwave Suzuki reaction, toluene, 150W; C: Stille reaction: Ph_4Sn, $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux; D: Sonogashira reaction: phenylacetylene, $Pd(PPh_3)_4$, CuI, THF/iPr_2EtN, reflux. E: Buchwald Hartwig reaction: piperidine, $Pd_2(dba)_3$, KHMDS, toluene; b) Obtained using two equivalents of phenylboronic acid.

3.6.3. Spectroscopic properties of the products

Both the unsubstituted and the substituted BODIPY dyes show spectroscopic properties similar to those of previously described boron dipyrromethene dyes, i.e. narrow bands of absorption and emission with small Stokes shifts. There is no significant influence of the substituents on the spectroscopic characteristics. A small hypsochromic shift of about 10 nm is visible with oxygen substituted dyes **229b** and **229c**, when compared to model dye **227c**. Again, the choice of the pyrrole moiety determines the properties of the resulting dye. By varying the substituents of the pyrrole ring, dyes with absorption and emission from green up to the near infrared can be obtained (Figure 8 and Table 28).

Figure 8. Normalized absorption (dash line) and fluorescence emission (solid line) spectra of **227a** (green), **227c** (pink) and **227d** (red) in THF.



Of particular interest is the fact that the fluorescence quantum yields Φ_f are high, and remain high in solvents of increasing polarity. This is presumably because of the hindered rotation of the *meso*-pyrimidyl ring by the 4',6'-substituents. Rotation of an aryl ring at the 8-position has been identified as one of the major pathways of nonradiative decay of the excited state, and this had been used to increase Φ_f by introducing bulky aryl groups or simply replacing the aryl substituent by hydrogen or a small alkyl chain.

Table 28. Spectroscopic data of selected BODIPY dyes in cyclohexane, THF, and acetonitrile

Product	Solvent	λ_{abs}(max)[a] / nm	λ_{em}(max)[b] / nm	$\Delta\bar{\nu}$ [c] / cm^{-1}	Φ_f
227a	Cyclohexane	518	537	683	0.98
	THF	517	537	720	0.66
	CH_3CN	514	532	658	0.68
227b	Cyclohexane	517	533	581	0.80
	THF	516	531	547	0.71
	CH_3CN	513	527	518	0.95
227c	Cyclohexane	579	608	824	0.58
	THF	575	607	917	0.57
	CH_3CN	568	602	994	0.71
227d	Cyclohexane	649	660	257	0.77
	THF	648	662	326	0.47
	CH_3CN	645	657	283	0.31
229b	Cyclohexane	570	600	877	0.79
	THF	570	602	933	0.74
	CH_3CN	560	593	994	0.91
229c	Cyclohexane	572	599	788	0.78
	THF	569	601	936	0.68
	CH_3CN	560	593	994	0.82
231a	Cyclohexane	580	606	740	0.82
	THF	579	607	797	0.57
	CH_3CN	570	603	960	0.68
231b	Cyclohexane	580	607	767	0.89
	THF	579	610	878	0.52
	CH_3CN	575	603	808	0.67
231c	Cyclohexane	574	602	810	0.75
	THF	573	604	896	0.63
	CH_3CN	565	603	1115	0.75
231d	Cyclohexane	578	605	772	0.60
	THF	578	607	827	0.62
	CH_3CN	568	601	967	0.75
231e	Cyclohexane	578	606	799	0.60
	THF	578	608	854	0.54
	CH_3CN	570	599	849	0.89

a) Absorption maximum. b) Fluorescence emission maximum. c) Stokes shift.

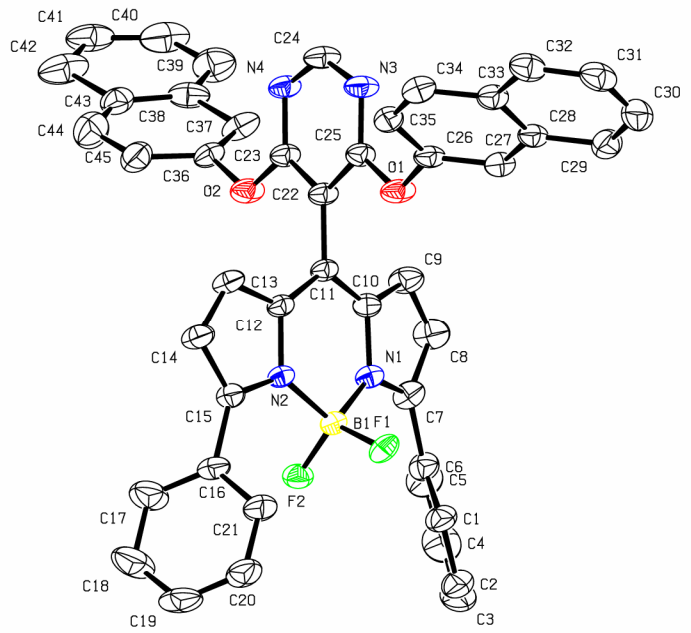
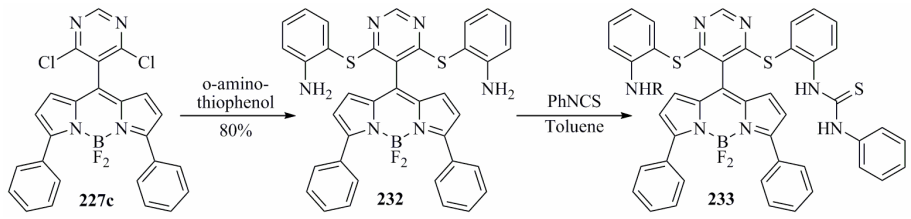


Figure 9. ORTEP representation of compound **229c** with displacement ellipsoids at the 20% probability level. A solvent molecule (CH_2Cl_2) and H atoms are omitted for clarity.

Further evidence of this restricted rotation could be found in an X-Ray analysis. As shown in Figure 9, the crystal structure of dinaphthyl dye **227c** is in line with most previously reported BODIPY dyes, with two planar pyrrole subunits and a boron atom forming a plane in the BODIPY ring system. The two fluorine atoms are equidistant above and below the plane of the pyrrole moieties, respectively, and the F-B-F plane is almost perpendicular (89.91°) to the plane of the BODIPY core. Moreover, the pyrimidine residues and the BODIPY core are linked to form an approximate orthogonal arrangement, with the angle between the plane composed by the BODIPY core atoms (B1, N1, C10, C11, C12, N2) and the pyrimidine ring (N3, C25, C22, C23, N4, C24) at 79.69°. Sterical interactions between the 4',6' substituents and the 1,7-hydrogen atoms make the rotation energetically strongly disfavoured.

Even though there is no general influence of the substituents on the spectral properties, we did encounter something peculiar. While looking for signs of electron transfer by substituting with an electron rich amine (**232**), a strong quenching of the fluorescence was observed. This decreased fluorescence is retained upon reaction with phenylisothiocyanate to thiourea **233**. So, there must be a way in which these substituents have a direct effect on the fluorescent core.

The exact nature of the effect is not yet known up to now, and further study is needed, especially as such thioureas have potential use in anion sensors.



Scheme 93. Placement of *o*-anilines on the dye leads to fluorophores with quenched fluorescence

3.6.4. Conclusion

We have developed a new and easily accessible BODIPY scaffold that can be substituted by nucleophilic aromatic substitution and by transition metal catalyzed cross coupling reactions. The spectral properties of the dyes do not depend on the introduced substituents, but can be related directly to the starting 8-(4,6-dichloropyrimidin-5-yl)-BODIPYs. In this fashion, reactive dyes with absorption and emission spectra throughout the visible spectrum are available as fluorescent probes and for labelling purposes.

3.7. Applications of reactive BODIPY systems

3.7.1. Fluorescent sensors

We have designed a range of reactive systems, which can be easily substituted. One obvious use of these systems is their application in the synthesis of fluorescent sensors. As the measurement of fluorescence response is a highly sensitive technique, this approach can be used to measure biologically relevant substrates.
Particularly, the possibility to introduce nitrogen nuclophiles at the 3,5-positions can be of interest as substitution at these positions directly influences the spectral properties of the dye. Therefore, such dyes have already been used for the preparation of fluorescent sensors. Currently, a major drawback of these sensors is the fact that they suffer from low quantum yields, and even though their quantum yields increase upon complexation, the total fluorescent response remains limited. Therefore, we set out to use our chemistry for the preparation of new and improved sensors.

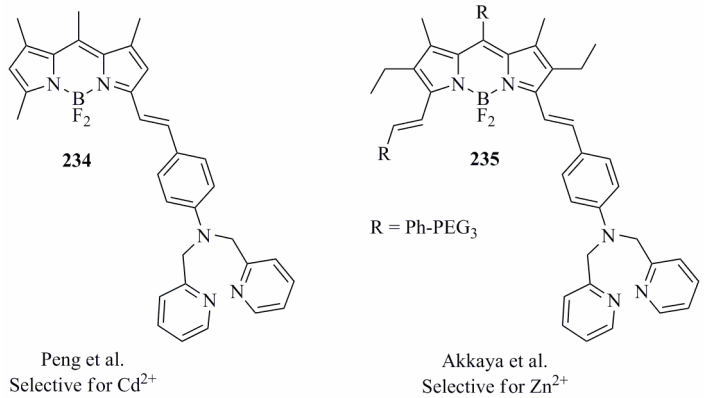
3.7.1.1. A fluorescent sensor for transition metal cations based on di-(2-picolyl)amine

Introduction and synthesis

Following literature examples, we chose *bis*(pyridin-2-ylmethyl)amine, commonly known as di-(2-picolyl)amine (DPA), as a chelator. This trisdentate ligand has been reported to form complexes with several metal ions, including Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Ag^{+}, Cd^{2+}, Hg^{2+} and Pb^{2+}.[104] Sensors combining DPA with BODIPY have been published for Zn^{2+} and Cd^{2+} ions.[110,111]
In the recent literature, a large number of fluorescent chemosensors for zinc ions have been reported based on different fluorophore platforms and various receptor units,[105] including DPA.[104, 106] Of significant importance for this study are reports on fluoroionophores based on the BODIPY core. Turfan and Akkaya[107] reported that the intense fluorescence of a BODIPY-dipyridyl

104 K. Kyose, H. Kojima, Y. Urano, T. Nagano, *J. Am. Chem. Soc.,* **2006**, 128, 6548.
105 (a) C. Fahrni, T. O'Halloran, *J. Am. Chem. Soc.* **1999**, 121, 11448; (b) Y. Mei, P. Bentley, *Biorg. Med. Chem. Lett.*, **2006**, 16, 3131.
106 (a) H. Wang, Q. Gan, X. Wang, L. Xue, S. Liu, H. Jiang, *Org. Lett.*, **2007**, 9, 4995; (b) S. Huang, R. Clark, L. Zhu, *Org. Lett.*, **2007**, *9*, 4999.
107 B. Turfan, E. Akkaya, *Org. Lett.*, **2002**, 4, 2857.

probe was quenched by Zn^{2+} via photoinduced electron transfer (PET)[108] from the excited BODIPY fluorophore to the dipyridyl subunit. The dissociation constant K_d for the 1:1 complex with Zn^{2+} was reported to be 90 pM, whereas the corresponding values for the Cd^{2+} and Hg^{2+} complexes were 50 μM and 0.6 mM, respectively. Zn^{2+} induced fluorescence quenching was also observed for terpyridine-functionalized BODIPY sensors.[109] A PET fluorescent sensor for Zn^{2+} (K_d = 1 nM) utilizing BODIPY linked at the *meso* position to the DPA chelator (Chart 1) which displays a significant fluorescence enhancement upon Zn^{2+} binding was described by Peng and coworkers.[25] The same research group also reported a selective sensor for Cd^{2+} built on the BODIPY platform **234** (K_d = ~60 μM), but with the DPA chelator attached at the 3-position via a *p*-styryl spacer.[110] A very similar BODIPY-styryl linked DPA chelator **235** was described by Akkaya and co-workers, but it was reported as being selective for Zn^{2+} (K_d = 20 μM), although Hg^{2+} and Cd^{2+} also showed some response.[111] While the probes of Peng[110] and Akkaya[111] are very similar, they display a different selectivity (Cd^{2+} vs. Zn^{2+}).

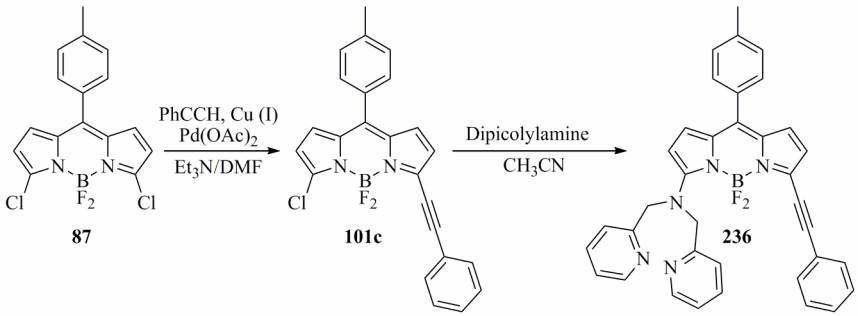


Scheme 94. Structural comparison between the DPA sensors described by Peng and Akkaya

Initial efforts to introduce the di-(2-picolyl)amine substituent on the 3-position of the BODIPY core were carried out with a 5-methoxy substituent. However, from preliminary spectroscopic characterization it was shown that the quantum yield was too low to be of use in a ratiometric sensor.

108 B. Valeur, *Molecular Fluorescence. Principles and Applications*; Wiley-VCH: Weinheim (Germany) **2002**.
109 C. Goze, G. Ulrich, L. Charbonnière, M. Cesario, T. Prangé, R. Ziessel, *Chem. Eur. J.*, **2003**, 9, 3748.
110 X. Peng, J. Du, J. Fan, J. Wang, Y. Wu, J. Zhao, S. Sun, T. Xu, *J. Am. Chem. Soc.*, **2007**, 129, 1500.
111 S. Atilgan, T. Ozdemir, E. Akkaya, *Org. Lett.* **2008**, 10, 4065.

Therefore, the methoxy substituent was replaced with a phenylacetylene, as this group has been shown to enhance the quantum yield strongly.
Synthesis of the target dye was straightforward, but hampered by purification problems of asymmetrical monochlorinated dye **101c**. Ultimately, the use of HPLC-purification did allow us to obtain the dye **101c**. S_NAr with di-(2-picolyl)amine proceeded in high yield, furnishing the compound **236** in an excellent yield.



Scheme 95. Synthesis of picolylamine based sensor for transition metals

Properties

Despite the phenylacetylene substituent, the sensor dye was only slightly fluorescent. As for the complexation behaviour, the transition metal ions Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Hg^{2+} produced spectral changes of **236** (
Table 29). For example, the lowest-energy absorption band of **236** shifts bathochromically by ~40 nm, from 525 nm in ion-free environment to 565 nm, when Zn^{2+} is added to the acetonitrile solution. The relative contributions of the 565/525 nm signals change with varying [Zn^{2+}] and the vis absorption spectra show isosbestic points at 434 and 540 nm. The maximum of the fluorescence emission band shifts bathochromically from 575 nm in ion-free acetonitrile to 584 nm in the presence of Zn^{2+} and is accompanied by an increase in intensity. The quantum yield Φ_f of **236** increases from 0.10 in the absence of Zn^{2+} to 0.29 for the **236**– Zn^{2+} complex.

Complex	λ_{abs}/ nm	λ_{em} /nm	Isobestic points / nm	K_d /μM	ν /cm^{-1}	Φ_f
236	525	575	-	-	1656	0.11
236-Ni^{2+}	565	580	540, 443	10.4	458	0.02
236-Cu^{2+}	594	616	547, 463	10.6	601	0.40
236-Zn^{2+}	565	584	540, 434	51.4	576	0.29
236-Cd^{2+}	575	590	540, 438	9.3	442	0.23
236-Hg^{2+}	575	590	537, 438	3.5	442	0.27
236-H^+	555	584	529, 409	3000	895	0.16

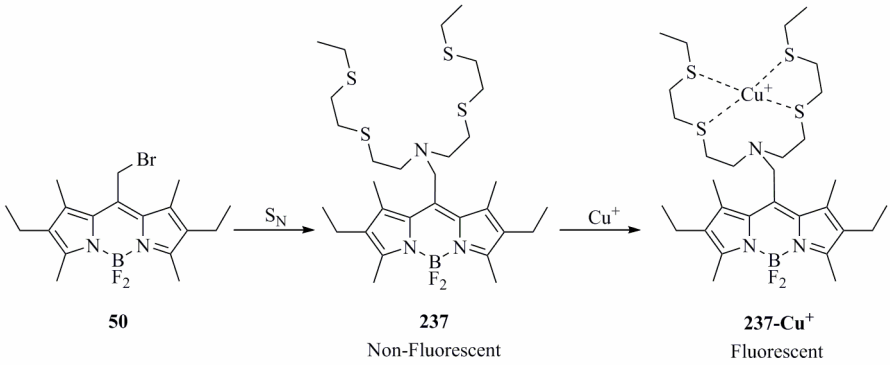
Table 29: Spectral characteristics of **236** in the absence and presence of transition metal ions (Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}) and H^+ in acetonitrile.

Upon addition of the alkali ions Na^+ and K^+ and the alkanine-earth ions Mg^{2+} and Ca^{2+} to a solution of **236** in acetonitrile, no change in the UV–vis absorption and fluorescence spectra could be detected. Obviously, the interaction between **236** and these ions is too weak to cause any change of either the UV–vis absorption spectra or the vis fluorescence spectra.

These results acknowledge the sometimes dubious results obtained with such sensors. Quantum yields for these dyes are generally low, and it takes a lot of synthetic effort to get them to acceptable levels. Furthermore, the selectivity of the ligands reported may not always be transferable to any given system.

3.7.1.2. A fluorescent sensor for copper(I) cations

In an attempt to show the potential of our reactive monochlorinated systems for the synthesis of fluorescent sensors, we were drawn to a few recent reports on Cu(I) sensing *in vivo*. As copper(I) is an unstable, transient species in oxidative processes in the cell, reliable tools for monitoring its presence are desirable. Therefore, Chang and co-workers used previously mentioned *meso*-bromomethyl BODIPY dyes **52** to attach a tetrathialigand to form sensor **239**. Electron donation of the lone pair from the nitrogen to the BODIPY renders the sensor non fluorescent, but upon complexation of Cu(I), fluorescence is restored.

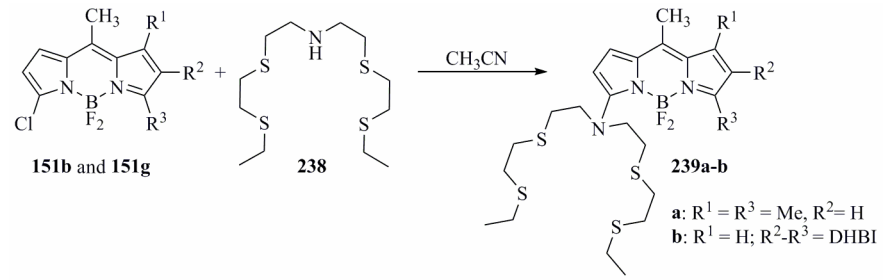


Scheme 96. Design and synthesis of a ON-OFF copper(I) sensor by Chan et al.

We reasoned that by placing the same ligand directly on the BODIPY core through nucleophilic aromatic substitution of monochlorinated fluorophores, ratiometric behaviour should be observed. Also, by changing the second pyrrole moiety, full control of the spectroscopic properties of the dye would be possible.

Synthesis

The target compounds were rapidly prepared by subjecting 3-chlorinated dyes **151b** and **151g** to amine **238** (Scheme 97). The amine is only poorly nucleophilic, and yields were therefore moderate. Immediately it was observed that the compounds are rather fluorescent, in line with spectroscopic results for amine model dye **152a**.

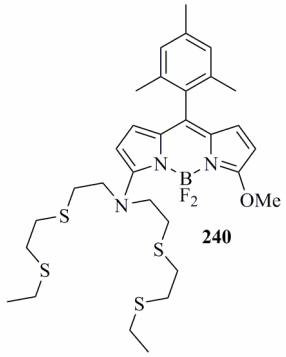


Scheme 97. Synthesis of ratiometric copper(I) sensors **239a** and **239b**

To our regret, while awaiting the results from the spectroscopic study, the group of Chang reported the use of a 3,5-dichlorinated system initially developed at our group[46] to prepare a sensor **240** with the thioether functionality linked at the 3-position.[112]

112 L. Zeng, E. Miller, A. Pralle, E. Isacoff, C. Chang, *J. Am. Chem. Soc.*, **2006**, 128, 10.

However, their compound suffers from the same problems mentioned in the beginning of this chapter. The combination of a 3-methoxy with a 5-nitrogen leads to compounds with poor quantum yields, and is therefore not very effective as ratiometric sensor. On the contrary, our nitrogen substituted systems still boast impressive quantum yields, and may therefore have use in superior ratiometric sensors.



Scheme 98. Ratiometric sensor for Cu(I) reported by Chang et al.

However, preliminary results show that compound **239a** does not only bind copper(I). Other soft metals such as silver and mercury also show significant effects. Again, a thorough literature study shows that the ligand and very similar structures have indeed been used in sensors for silver and mercury. This contrasting selectivity is fully is in line with what we observed for the dipicolyl sensor.

3.7.1.3. Conclusion

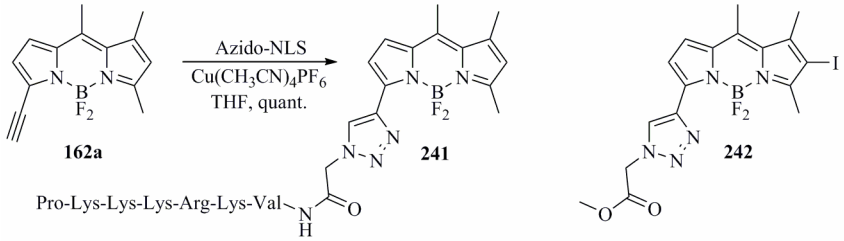
As shown by both examples, amine substitution at the 3-position of reactive BODIPY dyes is a highly interesting way of obtaining sensor activity. Nevertheless, the current sensors are often seriously lacking selectivity and therefore have little value outside the academic world. With all the reactive systems here presented, the crucial factor in sensor design is no longer the conjugation of fluorophore and sensor, but the use of truly selective ligand-fluorophore combinations.

3.7.2. BODIPY-NLS conjugates for photodynamic therapy

Photodynamic therapy is a non invasive therapeutic technique, based on organic sensitizers, light and molecular oxygen. Upon irradiation with visible or near-infrared light, the photosensitizer is excited from the ground state to an excited singlet state. This is followed by intersystem crossing to a triplet state. As molecular oxygen is present in the triplet state, energy transfer from the excited dye to the oxygen drives it to a singlet state. Singlet oxygen is a very reactive species and, when present in a living cell, it aggressively attacks any nearby biomolecules. Therefore, prolonged irradiation of living tissue that has been treated with the sensitizer leads to programmed cell death. Such treatments have been studied to target cancers, and several compounds have made it to the market, or are in advanced stages of clinical trials.
Sensitizers associated with PDT are mostly of the porphyrin type, or precursors thereto such as 5-amino-levulinic acid. Drawbacks of these systems are high dark-toxicity, low specificity for cancerous cells and poor singlet oxygen generation.
Recently, there have been efforts to translate the desired properties of a PDT sensitizer to BODIPY systems. This seems a highly interesting approach, as the non-toxic BODIPY dyes can be modified both spectroscopically and physicochemically to meet requirements.
However, as BODIPY dyes are noted for their fluorescence, they have very little triplet state formation. The introduction of halogen substituents has been extensively shown to induce this triplet state formation, and this is referred to as the "heavy atom effect".
We conceived a design where our reactive BODIPY dyes would be activated for photodynamic therapy by the placement of bromines or iodines on the correct positions. Subsequently, we would use the remaining reactive handle to link a nucleus targeting polypeptide sequence (NLS) to the dye. As such, the actual sensitizer would be transported to the cell nucleus, whereupon after irradiation, it could damage the DNA. Ideally, we could prove that targeting the nucleus rather than the cytoplasm leads to a higher cell toxicity or lower sensitizer loading needed to induce apoptosis of the malignant cells.

3.7.2.1. Results and discussion

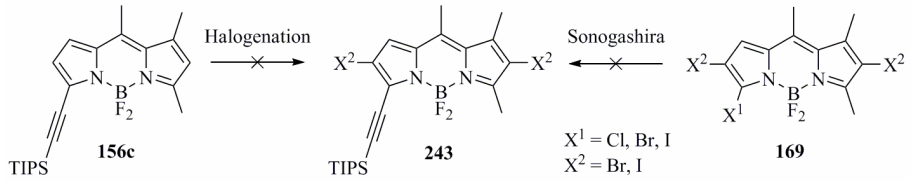
The initial strategy was based on copper(I) catalyzed triazole formation to link acetylene dye **162a** to an azide functionalized nucleus locating sequence. Reaction conditions were previously optimized, and we were pleased to observe conjugation of the model dye to the peptide sequence in quantitative yield. The resulting fluorescent peptide **239** was purified by HPLC and fully characterized.



Scheme 99. Copper catalyzed cycloaddition based ligation of a Nucleus Locating peptide Sequence (NLS) with alkyne BODIPY; and a monoiodinated model triazole synthesized using a similar protocol.

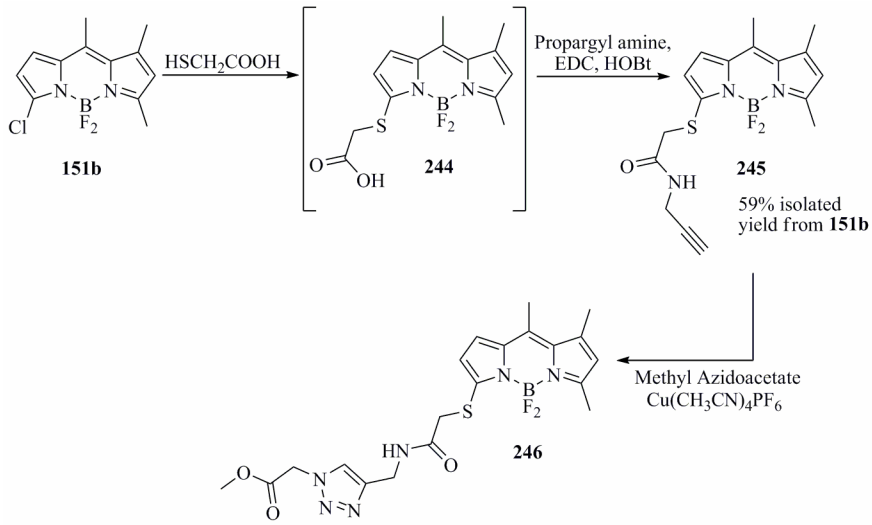
However, while trying to introduce heavy atoms to these acetylene systems, problems were encountered. As the initial route was to halogenate the TIPS-BODIPY **156c**, we observed rapid reaction with halide sources. Sadly, we were unable to purify the desired products from a mixture of dyes. It seems that that the alkyne suffers from halogenation as well, and after numerous attempts, this route was abandoned.

Halogenation prior to alkyne introduction was already tested (Scheme 66) and shown to proceed in high yield. These systems were subjected to Sonogashira coupling reaction with TIPS-acetylene. While this reaction was possible for the 3-chlorinated-6-halogenated dyes, coupling failed in the presence of a 2-halogen. Intermediates formed in this palladium catalyzed reaction must be unstable, and no product could be observed.



Scheme 100. Unsuccessful synthetic routes to 2,6-halogenated-3-alkynated BODIPY dyes

In a third route, the direct Sonogashira reaction was abandoned, and an amide coupling strategy was proposed. Nucleophilic substitution of 3-chlorinated model dye **151b** with 2-mercapto-acetic acid efficiently furnished acid **244**, which was converted in high yield to propargylic amide **245**. Copper catalyzed "click reaction" with the model azide (methyl azido-acetate) afforded triazole **246** in near quantitative yield. A similar reaction scheme is currently under way for the halogenation products.



Scheme 101. Thiolation of monochlorinated model dye **151b** followed by amidation and "click-reaction" with methyl azidoacetate to triazole **246**

3.7.2.2. Conclusion

Once a successful strategy for the ligation of halogenated alkyne BODIPY dyes and azides is fully disclosed, model triazolyl dyes like **242** and **246** will be assessed on their singlet oxygen generative power. Both halogen and halogenation pattern will be studied, and therefrom the optimal sensitizer will be selected. This sensitizer will then be linked to the Nucleus Locating peptide Sequence, and studied *in vivo* for both transport behaviour and activity in photodynamic therapy. By comparing the same BODIPY dye, with and without the peptide sequence, the effect of intranuclear location should be clear.

3.7.3. Boron difluoride as protecting group in the synthesis of complex dipyrrins.

3.7.3.1. Introduction and synthesis

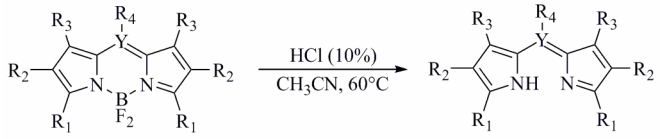
Dipyrrin or dipyrromethene ligands have been known for over a 100 years. However, research into their chemistry has been strongly limited by difficulties occurring during their synthesis. The preparation of these ligands often requires a background in the challenging field of pyrrole chemistry and involves highly unstable intermediates. Moreover, purification is difficult due to acid-base behaviour, and the resulting dipyrrins may have limited stability. Despite these drawbacks, a large amount of dipyrrin complexes and the use thereof in supramolecular structures, novel materials and biological systems has been reported.[5]

The most well known of these complexes is the borondifluoride complex of dipyrrins which has attracted a great deal of attention due to its fluorescent properties. Unlike its precursor dipyrrins, these complexes of boron, in this work referred to as BODIPY's, have developed a very rich chemistry. These compounds generally are highly stable and allow a wide range of reactions to tune the properties and applications of the dyes. They can be subjected to palladium catalyzed reactions, nucleophilic substitutions and condensations reactions, and this on virtually all possible positions. Because of this sharp contrast with the free base dipyrrin, a robust decomplexation protocol of the BODIPY dyes could provide a route towards unprecedented dipyrrin ligands. Porphyrins and corroles can be demetallated under acidic and reductive conditions,[113] and there have also been studies into the demetallation of metal complexes of the dipyrromethenes. For example, it has been shown that the removal of zinc, copper and palladium from a dipyrrin complex can be achieved by the mild reductive ligand DTT.[6] Stronger reductive conditions are also effective, but can reduce the dipyrrin to a dipyrromethane. Acidic conditions, like methanolic hydrochloric acid or trifluoroacetic acid also work, but lack generality.

Initial experiments showed that the dye shows excellent stability towards acidic conditions. Decomposition of the BODIPY core could be observed in concentrated trifluoroacetic acid, but decomplexation did not take place under mildly acidic conditions. Also, the use of reducing agents, like $LiAlH_4$, $NaBH_4$, $NaCNBH_3$ and DTT, had either no effect, or resulted in the formation of dipyrromethane and decomposition products.
A breakthrough appeared upon the application of the protocol used for the

113 J. Cowan, J. Sanders, *Tetrahedron Lett.*, **1986**, 27, 1201.

demetallation of corroles, using tin chloride in acetonitrile. Analysis of the reaction showed the formation of the corresponding dipyrrin, albeit after prolonged periods of time. As this method combines both acidic and reductive conditions a study was performed to asses the need for both these factors. From this study, the acid proved to be decisive and optimized conditions quantitatively yielded the dipyrrin after 3h at 60°C in 10% HCl (v/v) in acetonitrile. The dipyrrin was obtained in essentially pure state as its free base form after a neutralisation and extraction procedure. Performing the reaction at room temperature is also possible, but the reaction can take days to go to completion.
The generality of the method was proven by the application of this method to a small library of BODIPY dyes. All the reactions proceeded in quantitative yield, and the resulting dipyrrins were stable under the reaction conditions.



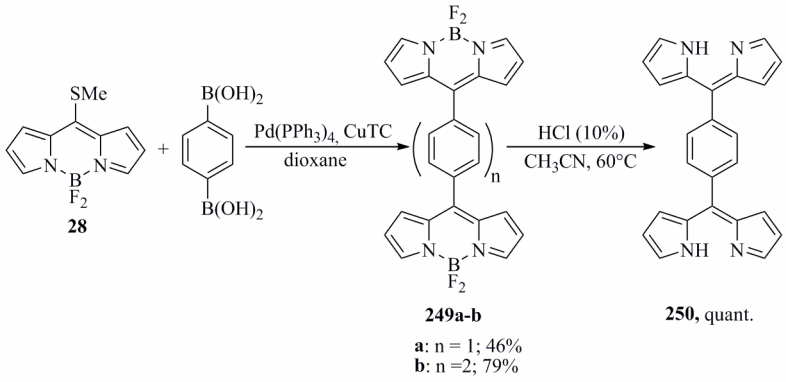
247 **248**

Table 30. Scope determination of the acid mediated deborylation

BODIPY	Dipyrrin	R^1	R^2	R^3	R^4	Y	Time	Yield
247a	**248a**	H	H	H	Ph	C	3h	Quant.[a]
247b	**248b**	H	H	H	4-Me	C	3h	Quant.[a]
247c	**248c**	H	H	H	4-MeOPh	C	3h	Quant.[a]
247d	**248d**	H	H	H	4-NO_2Ph	C	24h	Quant.[a]
247e	**248e**	Me	H	Me	4-MePh	C	3h	Quant.[a]
247f	**248f**	Ph	H	H	Ph	C	24h	Quant.[a]
247g	**248g**	DHBI		H	Me	C	6h	Quant.[a]
247h	**248h**	Ph	H	Ph	-	N	24h	92[a]

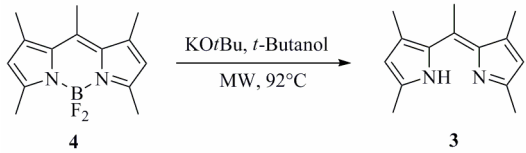
a) The reaction was assumed to proceed in quantitative yield as the isolated yield exceeded 96%, and no other products could be observed by TLC analysis. b) Purified by filtration over silica-pad due to insufficient solubility.

Finally, palladium catalyzed substitution of a *meso*-thiomethyl BODIPY **28** with a boronic acid, in a Liebeskind reaction, is a fast and easy way to prepare *meso* substituted BODIPY dyes. As the literature procedure uses a large excess of boronic acid, a slightly modified procedure allowed us to prepare *bis*-BODIPY's **249a-b** in good yield. Application of our deborylation procedure furnished the *bis*-dipyrrin **250** in quantitative yield. The synthesis of this product was the original reason for our research into this deprotection, as we could not prepare it in the conventional manner. Application of this ligand in dipyrrin complexes could lead to exciting new macromolecular architectures.



Scheme 102. Double Liebeskind cross-coupling followed by deborylation to yield *bis*-dipyrrin **248**

The attractiveness of such a deborylation approach is acknowledged by a recent report of Thompson et al., describing a similar protocol under basic conditions. Heating BODIPY dyes with excess of strong base under microwave irradiation leads to clean formation of the dipyrrins. The process appeared to be highly temperature dependent, with clean reactions at 92°C, but not at lower temperatures.



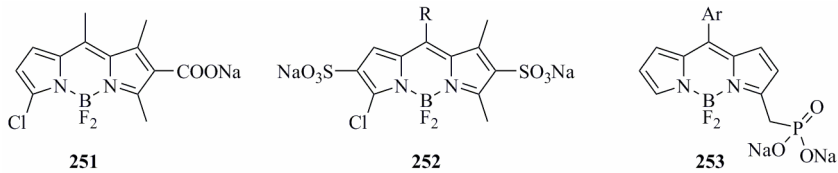
Scheme 103. Deborylation of BODIPY dyes under microwave irradiation in basic conditions

Conclusion

In conclusion, borondifluoride is a robust protecting group for BODIPY dyes. It can be introduced in high yield from complex mixtures of impure product, facilitating purification. The complex can then be subjected to a wide range of reactions, followed by liberation of the free base dipyrrin using a simple and general procedure.

4. General conclusion and outlook.

During this research towards the properties of reactive BODIPY dyes we have disclosed a range of novel systems.
By combining full control over the halogenation and thioetherification of the pyrrolic building blocks, fluorophores with reactive substituents at all possible positions were prepared. The reactivity of these systems was studied, and shown to be highly versatile. The compounds prepared showed very desirable spectral properties, such as high quantum yields of fluorescence and relatively high molar absorption coefficients. We believe that the ease of synthesis and the versatility of the substitution are major advantages. By changing to, or combining with, sulfur substituents, the reactivity can even be further optimized. In the end, these systems allow full control of the properties of the resulting dye. Not only spectroscopic properties can be changed to meet requirements, but functionality can be introduced in a single step.
As a major application of such dyes lies in biochemical research, the preparation and substitution of water soluble dyes remains a point of interest. Thereto, expanding the palladium chemistry and nucleophilic substitutions developed for the conventional dyes, to our 2,6-disulfonated dye is an option. However, it is of practical interest to introduce the water solubilizing, polar group at a late stage of the synthesis, and the use of ester or phosphonate ester functionalities as masked carboxylates and phosphates is another option.

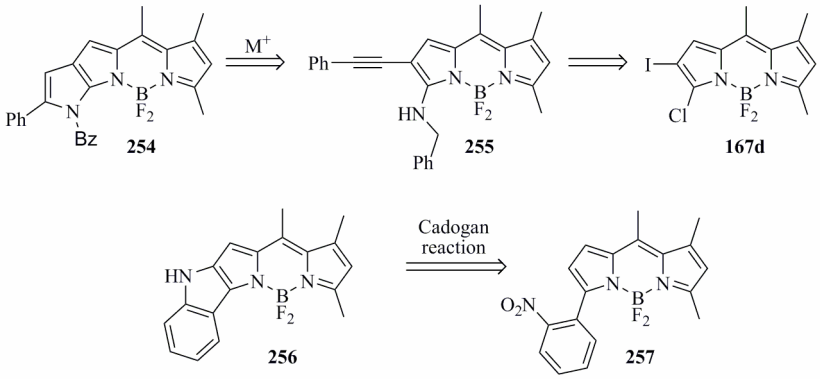


251 **252** **253**

Scheme 104. Some reactive water soluble BODIPY dyes

Then we introduced a short and high yielding approach to restricted BODIPY dyes to the field. Such a design bypasses tedious pyrrole synthesis and gives rise to red shifted fluorescent compounds. Unfortunately, up to now, this synthetic route has only been described for oxygen substituted dyes. Extending this strategy to the corresponding nitrogen and sulfur analogues should lead to near infrared emitting dyes. Other transition metal catalyzed ring formations, such as formation of a pyrrole **254** from alkyne **255** remain to be investigated.
As the quest for such dyes continues incessantly, modular approaches to the other isomers can be devised, starting from 3,5-disubstituted dyes or other halogenation patterns described. These other isomers have been shown to

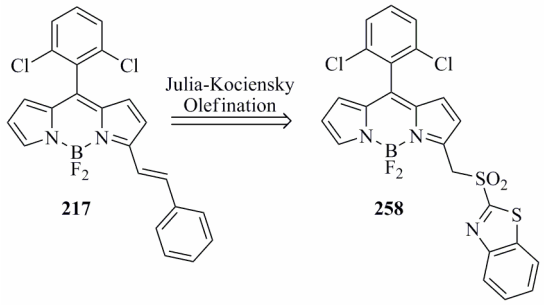
lead to even larger bathochromic shifts, combined with high quantum yields of fluorescence and extremely high molar absorption coefficients. The Cadogan reaction to indole **256** would be a plausible alternative, with the starting compound **257** originating from the monohalogenated dyes.



Scheme 105. Some proposed synthetic routes towards annelated nitrogen heterocycles

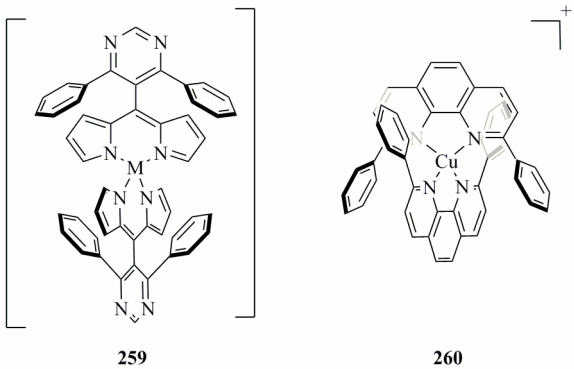
The oxidative substitution of the α-hydrogen of BODIPY dyes has been proven to be an excellent alternative to other, more conventional methods. Such a direct functionalization can start from readily available starting materials, and rapidly lead to complex systems. We are currently only scratching the surface, and a lot of applications remain to be uncovered. In our opinion, this route has the highest potential, as it totally avoids any unstable pyrrole intermediates. More research should be placed in the control of the regiochemistry of transition metal catalyzed direct substitution. Also, by expanding this approach to asymmetric dyes, a degree of control similar to our halogenated systems could be achieved.

As for the efforts to improve the condensation reaction between aromatic aldehydes and BODIPY dyes, a solution may be found in the Julia-Kociensky olefination. The starting material thereto **258** could be obtained from direct vicarious nucleophilic substitution of hydrogen, or decarboxylative functional group introduction (Scheme 105).



Scheme 106. Benzothiazole BODIPY dyes and Julia-Kociensky reaction as a solution for the low yielding olefination reactions

We have also extended these substitutions directly onto the BODIPY core, to systems with a reactive moiety not linked to the fluorescent system. However, the properties were not as expected, and therefore, the use of these systems remains limited. However, by combining the reactive pyrimidinyl substituent with other reactions, such as hydrogen substitution or deborylation, several interesting systems could be attained. For example, copper complex **259** is an analogue of the phenantroline complexes that have found extensive use in supramolecular chemistry, most notably in the work of Sauvage. [114]



Scheme 107. Copper complex of *meso*-pyrimidinyl dipyrrins as building block for supramolecular structures

In attempts to prove that our new methods can truly have applications, we described two new sensors for metal ions. Even though they do not show the selectivity originally hoped for, the entire strategy is not yet to be rejected. With some synthetic effort, more selective ligands could be prepared, and linked to the reactive dyes in a similar fashion. As such, selective sensors with a ratiometric response lie within reach.

114 J. Frey, T. Kraus, V. Heitz, J. Sauvage, *Chem. Commun*., **2005**, 42, 5310.

5. Experimental Data

Chemicals were purchased from Acros Organics, Sigma Aldrich and TCI Europe and used as received. Al reactions were carried out in flame dried glassware, but no special precautions were taken for the exclusion of moisture. Solvents were not dried prior to use, unless stated otherwise. All reactions were carried out under nitrogen, unless stated otherwise. Oxygen gas was 99.5% pure.

^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance 300 instrument operating at a frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C. In the case of ambiguous assignments, spectra were run on a Bruker 400 or Bruker 600. ^{1}H NMR spectra in $CDCl_3$ were referenced to tetramethylsilane (0.00 ppm) as an internal standard. ^{13}C NMR spectra in $CDCl_3$ were referenced to the $CDCl_3$ (77.67 ppm) signal. ^{1}H NMR spectra in CD_3CN were referenced to CH_3CN (1.94 ppm) as an internal standard. ^{13}C NMR spectra in CD_3CN were referenced to the CD_3CN (118.2 ppm) signal.

Due to the small coupling constants on pyrroles and pyrrolic dyes, the multiplicity of the signal is often unclear. In these cases, signal often appear as singlets, while they are not, and therefore, these signals are listed as multiplets (m).

Mass spectra were recorded on a Hewlett-Packard 5989A mass spectrometer (EI mode and CI mode). High-resolution mass data were obtained with a Kratos MS50TC instrument. Melting points were taken on a Reichert Thermovar and are uncorrected.

Absorption spectra were recorded on a Perkin Elmer Lambda 40. For the corrected steady-state emission spectra, a SPEX Fluorolog was used. Freshly prepared samples in 1-cm quartz cells were utilized to perform all UV–vis absorption and emission measurements. For the determination of the relative fluorescence quantum yields (Φ_f) in solution, only dilute solutions with an absorbance below 0.1 at the excitation wavelength were used. Rhodamine 6G in spectrograde ethanol (Fluka) was used as standard to determine the fluorescence quantum yields. All spectroscopic measurements were done at 20 °C.

8-Arylated BODIPY dyes were prepared according to standard literature procedures, through a water based dipyrromethane synthesis[115] and oxidation and condensation.[41]

2,4-Dimethylpyrrole is prepared using the Knorr-procedure,[116] or purchased from Acros Organics.

115 T. Rohand, E. Dolusic, T. Ngo, W. Maes, W. Dehaen, *ARKIVOC*, **2007**, 10, 307.
116 H. Fisher, *Org. Syn, Coll. Vol.*, **1943**, 2, 217.

5.1. General pyrrole synthesis

5.1.1. Trofimov reaction

In a Trofimov reaction, 2- or 2,3-substituted pyrroles are prepared from acetylene gas and oximes.[102] These pyrroles have been prepared by an adapted literature procedure, where the acetylene gas is prepared directly from calcium carbide (technical grade).

To a solution of a ketone in dimethylsulfoxide (approx. 2 ml / mmole) in a three-necked flask is added hydroxylamine hydrochloride (1 equiv.) and sodium hydrogen carbonate (1 equiv.). The mixture is stirred under an argon atmosphere overnight, while the oxime forms. (Careful: evolution of gas!).

Then, to a three-neck flask fitted with a reflux condenser, a septum and a closed valve, calcium carbide (approx 1gr per mmole of oxime) is added, and the setup is flushed with argon. The flask is immersed in an ice bath. The valve is connected to a gas washing bottle with rubber tubing. The outlet of the gas washing bottle is connected to the second three-necked flask, containing the oxime, with rubber tubing and an efficient needle.

Subsequently, the three-necked flask containing the oxime is fitted with a reflux condenser and a gas outlet valve on top of the condenser, and heated to 140°C using an oil bath. A fresh balloon filled with argon gas is placed on the flask containing the calcium carbide, and all of the closed valves are opened, resulting in the bubbling of argon through the dimethylsulfoxide solution. As the argon has blown out all of the carbon dioxide, and the argon balloon is empty, dropwise addition of water to the calcium carbide is started. When the entire setup is filled with acetylene gas, powdered KOH (1.5 equiv.) is added to the DMSO solution. The mixture is stirred at 140°C for the designated time (1 to 3 hours), cooled to room temperature and poured in diethyl ether/water. The solution is extracted with diethyl ether (3 times, special care should be taken in the case of water soluble pyrroles, such as 2-methyl pyrrole and 2,3-dimethyl pyrrole). The organic layers are combined and washed with water (3 times), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude pyrrole is purified chromatographically (Silica, petroleum ether until *N*-vinylpyrrole has eluted, and then petroleum ether: dichloromethane (1:1). All pyrroles are unstable and are therefore best stored under refrigeration.

Remaining unreacted calcium carbide can be hydrolyzed by carefully immersing the solid in water; the resulting suspension is kept overnight, and discarded as basic waste.

5.2. Halogenated BODIPY dyes

5.2.1. Synthesis of halogenated pyrroles

General synthesis of 2-acyl-5-halopyrroles:

CAUTION: This synthesis describes the preparation and handling of halogenated pyrroles. These compounds are highly unstable, and decompose rapidly and violently with the evolution of toxic gases. Always handle these compounds in a fume hood. Any remaining halopyrrole after reaction can be stabilized by the addition of a few drops of triethylamine to the reaction mixture just before evaporation.

Using sulfuryl chloride

A stirred solution of pyrrole (1.34 g, 1.4 ml, 20 mmol) in dry THF (100 ml) under nitrogen, is cooled to -78 °C. Sulfuryl chloride (2.70 g, 20 mmol) in THF (100 ml) is added dropwise. Gas evolution is observed, and the resulting solution is stirred at -78 °C for 3 hours. Next the acylating agent is added in a dropwise manner over 10 minutes and the resulting solution is stirred at room temperature for 14 h. An aqueous solution of Na_2CO_3 (100 mmol in 200 ml H_2O) is added and the reaction is refluxed for 30 minutes. The mixture is extracted with diethyl ether (3 × 100 ml), washed with saturated $NaHCO_3$ (2 × 200 ml or until basic) and water (2 × 300 ml or until neutral). The solution is dried over $MgSO_4$, filtered and evaporated under reduced pressure until dryness. The residue is purified chromatographically (Silica, CH_2Cl_2/ethyl acetate; 95:5, v/v) to yield the target pyrrole as a colourless crystalline solid.

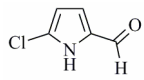
Note: The acylating agent can be prepared, as for any Vilsmeier reaction, by mixing 22 mmol of a dimethylamide or an *N*-morpholinoylamide and 22 mmol of $POCl_3$ at 0 °C and stirring at room temperature until the Vilsmeier reagent has formed. After formation of the salt, it is dissolved in CH_2Cl_2 (50 ml) prior to addition.
In the case of trichloroacetylation and trifluoroacetylation, the acylating agent constitutes of 20 mmol of trichloroacetyl chloride or trifluoroacetic acid anhydride, respectively, in 50 ml of THF. The hydrolysis can then be replaced by stirring with water/$NaHCO_3$.

Using N-chlorosuccinimide (NCS)

A stirred solution of pyrrole (1.34 g, 1.4 ml, 20 mmol) in THF (100 ml) under nitrogen is cooled to -78 °C. NCS (2.67 g, 20 mmol) is added

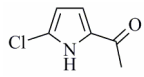
portionwise over 15 minutes. The resulting solution is stirred at -78 °C for 30 minutes and then placed in the freezer for 14 h. The cooled solution is then brought to 0 °C and stirred at this temperature for 6 h. Next, the acylating agent is added in a dropwise manner over 10 minutes and the resulting solution is stirred at room temperature for 14 h. An aqueous solution of NaOAc (70 mmol in 200 ml H_2O) is added and the reaction is refluxed for 30 minutes. The mixture is extracted with diethyl ether (3 × 100 ml), washed with saturated $NaHCO_3$ (2 × 200 ml or until basic) and water (2 × 300 ml or until neutral). The solution is dried over $MgSO_4$, filtered and evaporated under reduced pressure until dryness. The residue is purified chromatographically (Silica, CH_2Cl_2/ethyl acetate; 9:1, v/v) to yield the target pyrrole as colourless a crystalline solid.

2-Formyl-5-chloropyrrole 147a



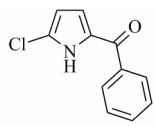
Using the general procedure, the compound is isolated as white crystals (1.010 g, 39 % yield).^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.89 (s, br, 1H, NH), 9.37 (s, 1H), 6.95 (q, 1H, J = 2.76 Hz, J = 3.52 Hz) 6.22 (q, 1H, J = 2.28 Hz, J = 3.76 Hz) ppm; ^{13}C-NMR: 178.5, 131.8, 126.5, 123.0, 110.1 ppm; LRMS (EI, 70 eV) m/z 128.

2-Acetyl-5-chloropyrrole 147b



Using the general procedure, the compound is isolated as white crystals (1.258 g, 44 % yield). Mp 78-81°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.67 (s, br, 1H, NH), 6.84 (d, 1H, J = 3.66 Hz), 6.11 (d, 1H, J = 3.66 Hz), 2.42 (s, 3H) ppm; ^{13}C-NMR: 187.1, 131.4, 123.4, 117.6, 109.2, 24.9 ppm; LRMS (EI, 70 eV) m/z 143; HRMS: calculated for C_6H_6ClNO 143.0138, found 143.0141.

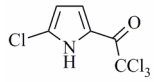
2-Benzoyl-5-chloropyrrole 147e



Using the general procedure, the compound is isolated as white crystals (10

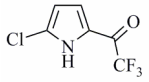
mmol scale, 670 mg, 33% yield). ^{1}H-NMR: δ 10.49 (s, br, NH), 7.89 (d, 2H, J = 7.29 Hz), 7.60 (t, 1H, J = 7.32 Hz), 7.48 (t, 2H, J = 7.29 Hz), 6.82 (d, 1H, J = 2.76 Hz), 6.20 (d, 1H, J = 3.66 Hz) ppm; ^{13}C-NMR: 184.0, 137.7, 132.2, 130.4, 129.1, 128.5, 124.4, 120.7, 109.6 ppm; LRMS (EI, 70 eV) m/z 205.

2-Trichloroacetyl-5-chloropyrrole 147d



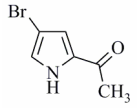
Using the general procedure from chloropyrrole and trichloroacetylchloride, the compound is isolated as white crystals (2.54 g, 52% yield). Caution: The compound is not stable in solution, and should be stored under refrigeration. Mp 79-81°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.56 (s, br, 1H, NH), 7.33 (s, t, J = 1.76 Hz), 6.25 (t, 1H, J = 2 Hz) ppm; ^{13}C-NMR: δ 172.4, 125.8, 122.4, 122.3, 110.6, 94.5 ppm.

2-Trifluoroacetyl-5-chloropyrrole 147c



Using the general procedure, the compound is isolated as white crystals (2.509 g, 64 % yield). ^{1}H-NMR: δ 9.81 (s, br, 1H, NH), 7.17 (m, 1H), 6.30 (m, 1H) ppm; ^{13}C-NMR: 169.6, 128.6, 125.2, 123.0, 122.9, 118.7, 114.9, 111.5 ppm; LRMS (EI, 70 eV) m/z 197; HRMS: calculated for $C_6H_3ClF_3NO$ 196.9855 found 196.98663.

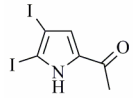
General procedure for the preparation of 2-acetyl-4-halopyrroles and 2-acetyl-4,5-dihalopyrroles with Oxone/Sodium halide: 2-Acetyl-4-bromopyrrole 149b



Acetylpyrrole (10 mmol, 1.44 gram) is dissolved in methanol (10 ml, 1 M solution) under nitrogen, followed by the addition of sodium bromide (1.3 gram, 10 mmol, 1 equiv.) in water (10 ml; final concentration 0.5 M). To the resulting solution, potassium peroxomonosulfate (3.837 g, 6.25 mmol, 0.625 equivs.) is added, and the mixture is stirred at room temperature for 30 minutes. A solution of sodium thiosulfate is added to remove any remaining halogen, followed by extraction of the aqueous solution with

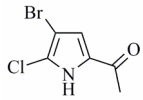
dichloromethane (3 x 100 ml). The combined organic layers are collected, dried on $MgSO_4$, filtered and evaporated to dryness. After column chromatography (Silica, CH_2Cl_2/Ethyl acetate; 9:1, v/v) the desired pyrroles are obtained as white solids. (1.552 g, 83 % yield). Mp 105°C; ^{1}H-NMR (400 MHz): δ 9.82 (s, br, NH), 7.02 (q, 1H, J = 1.28 Hz, J = 2.76 Hz), 6.89 (q, 1H, J = 1.28 Hz, J = 2.24 Hz), 2.41 (s, 3H) ppm; ^{13}C-NMR: 187.6, 133.5, 129.9, 123.6, 25.6 ppm (one pyrole signal not observed); LRMS (EI, 70 eV) m/z 188.

2-Acetyl-4,5-diiodopyrrole 166c



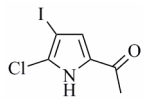
After the general halogenation procedure with doubled amounts of halide and oxone, the compound is filtered from the reaction mixture as white crystals (2.775 g, 77% yield). Mp 160°C; ^{1}H-NMR: δ 9.82 (s, br, 1H, NH), 6.92 (d, 1H, J = 2.64 Hz), 2.40 (s, 3H) ppm; ^{13}C-NMR: 186.1, 138.0, 124.0, 86.9, 77.3, 25.0 ppm; LRMS (EI, 70 eV) m/z 380.

2-Acetyl-4-bromo-5-chloropyrrole 166b



Using the general procedure, but starting from 4-bromo-2-acetylpyrrole, the compound is isolated as white crystals (5 mmole scale, 970 mg, 87% yield). Mp 113°C; ^{1}H-NMR: δ 11.12 (s, br, 1H, NH), 6.89 (s, 1H), 2.42 (s, 3H) ppm; ^{13}C-NMR: 187.3, 130.3, 123.9, 119.4, 96.8, 25.0 ppm; LRMS (EI, 70 eV) m/z 224.

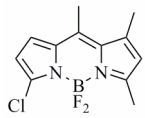
2-Acetyl-4-iodo-5-chloropyrrole 166d



Using the general procedure, but starting from 4-iodo-2-acetylpyrrole, the compound is isolated as white crystals (5 mmole scale, 877 mg, 65% yield). Mp 122°C; ^{1}H-NMR δ 10.8 (s, br, 1H, NH), 6.97 (s, 1H), 2.41 (s, 3H) ppm; ^{13}C-NMR: 186.8, 132.4, 127.9, 124.3, 116.4, 25.0 ppm; LRMS (EI, 70 eV) m/z 269.

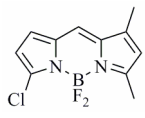
5.2.2. Synthesis of halogenated BODIPY dyes

Condensation of selected pyrroles to corresponding BODIPY, general procedure: 3-Chloro-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 151b



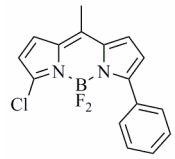
2-Acetyl-5-chloropyrrole (5 mmol, 670 mg) is dissolved in a mixture of 4 ml CH_2Cl_2 and 2ml pentane and stirred under nitrogen. 2,4-Dimethylpyrrole (620 µl, 5 mmol, 1 equiv.) is added and the resulting solution is cooled to 0 °C using an ice bath, followed by the addition of $POCl_3$ (470 µl, 5 mmol, 1 equiv.). The solution is stirred at room temperature for 6 h. During this period the mixture turns dark. Triethylamine (7 ml, 50 mmol) is added and the mixture is stirred for 10 minutes, and cooled to 0 °C. Boron trifluoride etherate (7 ml, 55 mmol) is added dropwise, and the reaction mixture is then stirred at room temperature for 1 h. The orange solution is poured in diethyl ether (400 ml) and extracted with water (3 × 200 ml). The ethereal solution is dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product is purified chromatographically (Silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield brick-red crystals (964 mg, 72%). Mp 228-230 °C. ^{1}H-NMR: δ 7.03 (d, 1H, J = 3.63 Hz), 6.29 (d, 1H, J = 3.66 Hz), 6.17 (s, 1H), 2.58 (s, 3H), 2.50 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C-NMR: δ 160.8, 145.6, 140.3, 137.3, 134.2, 133.3, 124.0, 123.4, 115.3, 16.9, 15.8, 15.0 ppm; LRMS (EI, 70 eV) m/z 268; HRMS: calculated for $C_{12}H_{12}BClF_2N_2$ 268.07501, found 268.07482.

3-Chloro-5,7-dimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 151a



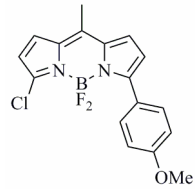
Obtained according to the general condensation procedure in 90% yield, as bright orange solid. Mp 162°C; ^{1}H-NMR: δ 7.01 (s, 1H), 6.80 (d, 1H, J = 3.76 Hz), 6.23 (d, 1H, J = 3.76 Hz), 6.13 (s, 1H), 2.56 (s, 3H), 2.20 (s, 3H) ppm; ^{13}C-NMR: δ 163.6, 145.9, 138.3, 136.4, 132.0, 126.7, 123.4, 121.7, 115.8, 15.2, 11.3 ppm; LRMS (EI, 70 eV) m/z 254; HRMS: calculated for $C_{11}H_{10}BClF_2N_2$ 254.05936, found 254.06083.

3-Chloro-5-phenyl-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 151e



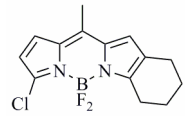
Obtained according to the general condensation procedure in 36% yield, as a purple solid. Mp 162-165°C; ^{1}H-NMR: δ 7.91-7.88 (m, 2H), 7.48-7.45 (m, 3H), 7.35 (d, 1H, J = 3.21 Hz), 7.16 (d, 1H, J = 3.21 Hz), 6.67 (d, 1H, J = 3.21 Hz), 6.37 (d, 1H, J = 3.21 Hz), 2.55 (s, 3H) ppm; ^{13}C-NMR: δ 160.3, 141.8, 133.9, 132.2, 130.0, 129.6; 129.5, 129.5, 129.0, 128.4, 126.5, 117.5, 15.5 ppm; LRMS (EI, 70 eV) m/z 316; HRMS: calculated for $C_{16}H_{12}BClF_2N_2$ 316.07501, found 316.07492.

3-Chloro-5-(p-methoxyphenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 151f



Obtained according to the general condensation procedure in 35% yield, as a purple solid; Mp 164°C; ^{1}H-NMR: δ 7.92 (d, 2H, J = 6.67 Hz), 7.34 (d, 1H, J = 4.17 Hz), 7.19 (d, 1H, J = 3.78 Hz), 6.99 (d, 2H, J = 8.67 Hz), 6.69 (d, 1H, J = 3.96 Hz), 6.34 (d, 1H, J = 3.78 Hz), 3.86 (s, 3H), 2.53 (s, 3H) ppm; ^{13}C-NMR: δ 161.3, 160.6, 140.4, 140.0, 137.5, 133.5, 131.3, 125.4, 124.4, 121.3, 116.8, 1147.0, 55.4, 15.4 ppm; MS (EI, 70 eV) 346; HRMS: Calculated for $C_{17}H_{14}ON_2BF_2Cl$ 346.0855, found 346.0866.

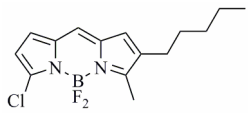
3-Chloro-5,6-cyclohexano-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 151d



Obtained according to the general condensation procedure in 31% yield, as a red solid. Mp 174-175°C; ^{1}H-NMR: δ 6.96 (s, 2H), 6.27 (d, 1H, J = 3.66 Hz), 3.09 (t, 2H, J = 6.39 Hz), 2.58 (t, 2H, J = 6.39 Hz), 2.44 (s, 3H), 1.85

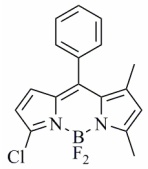
(m, 2H), 1.75 (m, 2H) ppm; ^{13}C-NMR: δ 162.8, 139.2, 137.8, 135.7, 133.3, 131.9, 125.9, 124.0, 115.3, 25.1, 23.3, 22.6, 22.1, 15.1 ppm; LRMS (EI, 70 eV) m/z 294; HRMS: calculated for $C_{14}H_{14}BClF_2N_2$ 294.09066, found 294.09051.

3-Chloro-5-methyl-6-pentyl-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



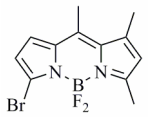
Obtained according to the general condensation procedure in 55% yield, as a red solid. Mp 59°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.92 (s, 1H), 6.80 (s, 2H), 6.25 (d, 1H, J = 3.28 Hz), 2.57 (s, 3H), 2.37 (t, 2H, J = 7.56 Hz), 1.55 (m, 2H), 1.33 (s, 3H), 0.92 (m, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 163.3, 138.5, 137.1, 135.4, 132.3, 129.7, 126.7, 125.3, 115.7, 115.7, 31.4, 28.8, 25.7, 22.4, 13.9, 13.3 ppm; LRMS (EI, 70 EV): 310.

3-Chloro-5,7-dimethyl-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 151c



Obtained according to the general condensation procedure in 43% yield, as a dark yellow solid. Mp 137-140°C; ^{1}H-NMR: δ 7.49-7.47 (m, 3H), 7.30 (d, 2H, J = 7.29 Hz), 6.31 (d, 1H, J = 3.66 Hz), 6.23 (d, 1H, J = 3.66 Hz), 6.14 (m, 1H), 2.63 (s, 3H), 1.51 (s, 3H) ppm; ^{13}C-NMR: δ 162.7, 147.1, 141.8, 138.3, 133.8, .133.5, 133.2, 129.6, 128.9, 128.6, 127.3, 123.8, 115.7, 15.3, 15.0 ppm; LRMS (EI, 70 eV) m/z 330; HRMS: calculated for $C_{17}H_{14}BClF_2N_2$ 330.09066, found 330.09052.

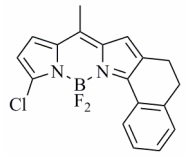
3-Bromo-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



Obtained according to the general condensation procedure in 62% yield, as a bright orange solid. Mp 219-220°C; ^{1}H-NMR: δ 6.99 (d, 1H, J = Hz), 6.40

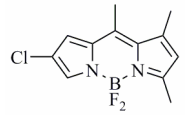
(d, 1H, J = Hz), 6.18 (m, 1H), 2.58 (s, 3H), 2.50 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C-NMR: δ 161.1, 160.8, 140.0, 135.0, 134.3, 124.1, 123.6, 119.1, 17.0, 15.8, 15.1 ppm; LRMS (EI, 70 eV) m/z 312; HRMS: calculated for $C_{12}H_{12}BBrF_2N_2$ 312.02450, found 312.02444.

3-Chloro-[5,6]-dihydronaphtyl-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 151g



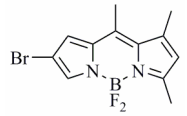
Obtained according to the general condensation procedure in 30% yield, as a dark shiny solid. Mp 185°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.73 (d, 1H, J = 7.28 Hz), 7.40-7.25 (m, 5H), 6.31 (s, 1H), 2.89 (m, 2H), 2.72 (m, 2H), 2.46 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 155.7, 141.3, 138.7, 137.6, 137.3, 134.2, 133.5, 130.9, 129.1, 129.0, 128.9, 128.5, 127.7, 127.5, 124.8, 124.2, 116.2, 30.4, 22.4, 15.4 ppm; LRMS (EI, 70 EV): 342; HRMS: Calculated for $C_{18}H_{14}BClF_2N_2$ 342.0907, found 342.09103.

2-Chloro-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 152a



Obtained according to the general condensation procedure in 36% yield, as an orange solid. Mp 198-199°C; ^{1}H-NMR: δ 7.44 (s, 1H), 6.92 (s, 1H), 6.21 (s, 1H), 2.58 (s, 3H), 2.52 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C-NMR: δ 162.6, 147.1, 141.4, 135.0, 133.8, 132..9, 123.7, 120.4, 118.7, 17.1, 16.3, 15.2 ppm; LRMS (EI, 70 eV) m/z 268; HRMS: calculated for $C_{12}H_{12}BClF_2N_2$ 268.07501, found 268.07547.

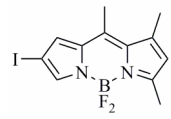
2-Bromo-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 152b



Obtained according to the general condensation procedure in 69% yield, as a bright orange solid. Mp 178-180°C; ^{1}H-NMR: δ 7.48 (s, 1H), 7.02 (s, 1H), 6.22 (s, 1H), 2.58 (s, 3H), 2.53 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C-NMR: δ 162.6,

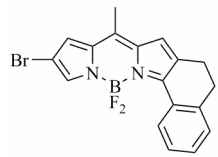
147.2, 141.1, 135.8, 134.9, 133.7, 123.8 123.1, 102.8, 17.0, 16.2, 15.1 ppm; LRMS (EI, 70 eV) m/z 312; HRMS: calculated for $C_{12}H_{12}BBrF_2N_2$ 312.02450, found 312.02453.

2-Iodo-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 152c



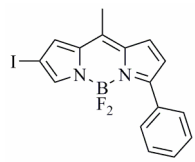
Obtained according to the general condensation procedure in 40% yield, as an orange solid. Mp 176-178°C; ^{1}H-NMR: 7.51 (s, 1H), 7.09 (s, 1H), 6.21 (s, 1H), 2.56 (s, 3H), 2.47 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C-NMR: 162.4, 147.1, 140.9,140.7, 135.4, 134.7, 128.7, 123.9 ,17.1, 16.3, 15.2 ppm; LRMS (EI, 70 eV) m/z 360; HRMS: calculated for $C_{12}H_{12}BF_2IN_2$ 360.01063, found 360.00963.

2-Bromo-[5,6]-dihydronaphthyl-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 152e



Obtained according to the general condensation procedure in 59% yield, as a purple solid. Mp 178-180°C; ^{1}H-NMR: δ 8.66 (d, 1H, J = 7.53 Hz), 7.53 (s, 1H), 7.42-7.34 (m, 2H), 7.27 (s, 1H), 7.11 (s, 1H), 6.95 (s, 1H), 2.90 (t, 2H, J = 7.17 Hz), 2.70 (t, 2H, J = 7.17 Hz), 2.43 (s, 3H) ppm; ^{13}C-NMR: δ 157.2, 141.7, 139.5, 137.9, 136.8, 134.7, 133.7, 131.4, 129.2-129.0 (t), 129.0, 129.6, 127.6, 127.0, 126.0, 123.0, 103.6, 30.2, 22.2, 15.8 ppm; LRMS (EI, 70 eV) m/z 386; HRMS: calculated for $C_{18}H_{14}BBrF_2N_2$ 386.04015, found 386.04007.

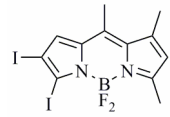
2-Iodo-5-phenyl-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 152f



Obtained according to the general condensation procedure in 25% yield, as a purple solid. Mp 123-125°C; ^{1}H-NMR: 7.94-9.89 (m, 2H), 7.63 (s, 1H), 7.48-7.46 (m, 3H), 7.42 (d, 2H, J = 4.32 Hz), 7.26 (s, 1H), 6.72 (d, 1H, J =

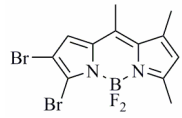
4.32 Hz), 2.56 (s, 3H) ppm; ^{13}C-NMR: 161.7, 144.2, 142.6, 137.9, 135.7, 131.7, 131.0, 130.6, 130.5, 129.6, 129.59, 129.56, 128.5, 121.8, 16.1 ppm; LRMS (EI, 70 eV) m/z 408; HRMS: calculated for $C_{16}H_{12}BF_2IN_2$ 408.01063, found 408.01072.

2,3-Diiodo-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 167c



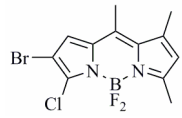
Obtained according to the general condensation procedure in 35% yield, as a red solid. Mp 195°C; ^{1}H-NMR (CD_2Cl_2, 300 MHz): δ 6.98 (s, 1H), 6.16 (s, 1H), 2.45 (s, 3H), 2.29 (s, 6H) ppm; ^{13}C-NMR (CD_2Cl_2, 75 MHz): δ 163.8, 148.1, 139.2, 139.0, 135.3, 129.5, 124.9 (q), 101.4, 58.1 (q), 17.3, 16.0, 15.4 ppm; LRMS (EI, 70 EV): 486.

2,3-Dibromo-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 167a



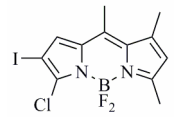
Obtained according to the general condensation procedure in 36% yield, as an orange solid. Mp 185°C; ^{1}H-NMR: δ 6.95 (s, 1H), 6.21 (s, 1H), 2.57 (s, 3H), 2.39 (s, 6H) ppm; ^{13}C-NMR δ 163.1, 147.1, 139.2, 134.8, 134.1, 124.3, 123.3, 123.1, 103.3, 103.5,17.0, 15.5, 15.2 ppm; LRMS (EI, 70 EV): 392.

2-Bromo-3-chloro-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 167b



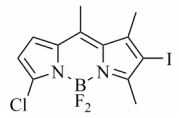
Obtained according to the general condensation procedure in 47% yield, as an orange solid. Mp 203°C; ^{1}H-NMR: δ 6.97 (s, 1H), 6.21 (s, 1H), 2.557 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C-NMR: δ 162.9, 147.0, 139.5, 134.7, 132.0, 124.1, 123.3, 102.7, 17.0, 15.5, 15.1 ppm; LRMS (EI, 70 EV): 347.

2-Iodo-3-chloro-5,7,8-Trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 167d



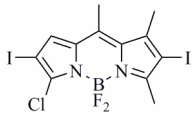
Obtained according to the general condensation procedure in 55% yield, as a brick-red solid. ^{1}H-NMR: δ 7.10 (s, 1H), 6.23 (s, 1H), 2.58 (s, 3H), 2.45 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C-NMR: δ 162.8, 146.9, 139.3, 139.2, 134.6, 134.4, 129.3, 124.3, 17.1, 15.6, 15.2 ppm; LRMS (EI, 70 EV): 394; HRMS: Calculated for $C_{12}H_{11}BClF_2IN_2$: 393.9717, found 393.97307.

3-Chloro-6-iodo-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 168c



Monochlorinated BODIPY dye **151b** (268 mg, 1 mmole) is dissolved in DCM (10 ml, 0.1 M). $NaHCO_3$ (168 mg, 2 mmole, 2 equivs.) is added, and the mixture is cooled to 0°C. Iodine monochloride (1 mmole, 1 ml of a 1M solution, 1 equiv.) is added dropwise. The solution is stirred at room temperature for 1h, and the reaction is quenched with $Na_2S_2O_3$. The mixture is extracted with dichloromethane and water, and after standard workup of the organic layers, the crude mixture is purified chromatographically (Silica, DCM/ Petroleum ether; 1:1; v/v). Red crystals; Mp 157°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.06 (s, 1H), 6.29 (s, 1H), 2.63 (s, 3H), 2.43 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 159.5, 146.1, 140.8, 139.1, 133.4, 133.2, 126.0, 116.3, 87.2, 22.1, 19.2, 16.7 ppm; LRMS (EI, 70 EV): 393.

3-Chloro-2,6-iodo-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 168d



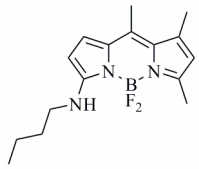
Obtained through the abovementioned procedure, but with two equivalents of iodine monochloride, as a shiny red solid. Mp 240°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.24 (s; 1H), 2.68 (s, 3H), 2.52 (s, 3H), 2.46 (s, 3H) ppm. No fully resolved ^{13}C spectrum obtained due to low solubility.

5.2.3. Nucleophilic substitution of monohalogenated BODIPY dyes

General procedure for the nucleophilic aromatic substitution with nucleophiles.

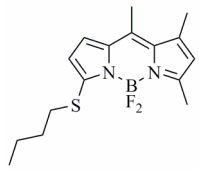
To a solution of BODIPY dye **151b** (27 mg, 0.1 mmole) in acetonitrile (1 ml) is added the nucleophile (1.3 equivalents), followed by the addition of base (1.3 equivalents). The resulting mixture is stirred at reflux until TLC analysis showed complete consumption of the starting material. The reaction mixture is poured in diethyl ether (100 ml), and extracted with $NaHCO_3$(aq.) (2 x 100 ml) and water (2 x 100 ml). The organic layer is dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. The compounds were purified chromatographically.

3-*N*-Butylamino-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 153b



Obtained according to the general nucleophilic substitution procedure, after purification by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v). Orange solid; No crystals obtained; ^{1}H-NMR: δ 7.19 (d, 1H, J = 4.76 Hz), 5.98 (d, 1H, J = 4.8 Hz), 5.89 (m, 2H, CH coinciding with NH), 3.32 (q, 2H, J = 6.8 Hz; J = 13.3 Hz), 2.44 (s, 3H), 2.38 (s, 3H), 2.34 (s, 3H), 1.64 (m, 2Hz), 1.46 (m, 2H), 0.94 (t , 3H, J = 7.28 Hz) ppm; ^{13}C-NMR: δ 159.9, 144.7, 133.0, 132.0, 131.3, 130.6, 129.6, 117.6, 106.4, 44.2, 32.2, 19.9, 16.0, 15.7, 14.0, 13.8 ppm; MS (EI, 70 eV) 305; HRMS: Calculated for $C_{16}H_{22}N_3BF_2$ 305.1875 , found 305.18858.

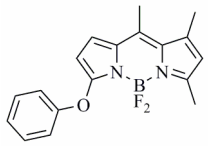
3-*S*-Butylsulfenyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 153c



Obtained according to the general nucleophilic substitution procedure,

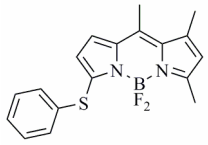
purified by column chromatography (Silica; Diethyl ether: Petroleum ether (1:3, v/v). Dark orange solid; Mp 95-97°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.11 (d, 1H, J = 4.28 Hz), 6.34 (d, 1H, J = 4.28 Hz), 6.07 (s,1H), 3.04 (t, 2H, J = 7.32 Hz), 2.54 (s, 3H), 2.47 (s, 3H), 2.37 (s, 3H), 1.75 (q, 5H), 1.51 (m, 2H), 0.94 (t, 3H, J = 7.32 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 156.2, 153.2, 142.0, 127.7, 125.7, 132.8, 125.5, 121.6, 115.0, 32.6, 31.0, 21.9, 16.5, 16.1, 14.6, 13.6 ppm; LRMS (EI, 70 EV): 322; HRMS: Calculated for $C_{16}H_{21}N_2SBF_2$ 322.14866, found 322.14875.

3-*O*-Phenyloxy-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 153e



Obtained according to the general nucleophilic substitution procedure, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v), second column: Silica; Diethyl ether: Petroleum ether (1:2, v/v)). Orange solid; Mp 90°C; ^{1}H-NMR: δ 7.42 (t, 1H, J = 7.92 Hz), 7.28 (m, 4H), 7.10 (d, 1H, J = 4.05 Hz), 6.08 (s, 1H), 5.64 (d, 1H, J = 4.35 Hz), 2.55 (s, 3H), 2.49 (s, 3H), 2.41 (s, 3H) ppm; LRMS (EI, 70 EV): 326; HRMS: Calculated for $C_{18}H_{17}BF_2N_2O$ 326.1402, found 326.13891.

3-*S*-Phenylsulfenyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-sindacene 153f



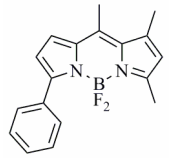
Obtained according to the general nucleophilic substitution procedure, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)) Red solid; ^{1}H-NMR: δ 7. 57 (m, 2H), 7.36 (m, 3H), 6.94 (d, 1H, J = 4.32 Hz), 6.06 (s, 1H), 5.64 (d, 1H, J = 4.17 Hz), 2.54 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H) ppm; LRMS (EI, 70 EV): 342.

5.2.4. Palladium catalyzed functionalization

General remarks on the application of transition metal catalyzed reactions to BODIPY dyes

- All reagents are air weighed. Solvents are not degassed prior to use, and are commercial *pro analyse* grade.
- All test reactions are carried out at a 0.1 M concentration. Upon optimization of the protocols, more concentrated solutions have often led to solubility issues.
- Reactions at the 3-position are relatively slow, and therefore all test reactions were conducted with 10% of palladium catalyst. However, once a protocol is established, catalyst loadings in large scale reactions are often successfully reduced to 2.5% without substantial changes in reaction times or yields. This has been the case for Stille, Heck and Sonogashira reactions.
- All palladium catalyzed coupling reactions at the 2-position are prone to dehalogenation. Superior yields are obtained with loadings under 1%.

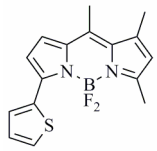
General procedure for Stille reaction: 3-Phenyl-5,7-dimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 154a



Monochlorinated BODIPY **151b** (27 mg, 0.1 mmol) is dissolved in toluene. Phenyl tributyltin (47 mg, 42 µl, 0.13 mmole, 1.3 equiv.), $Pd(PPh_3)_4$ (11 mg, 0.1 mmole, 10 mole%) and Na_2CO_3 (16 mg, 0.15 mmole, 1.5 equiv) are added and the mixture is flushed with nitrogen. The reaction mixture is heated to reflux for 14h, followed by evaporation of the solvent. The crude mixture is purified chromatographically (Silica; DCM/ Petroleum ether; 1:1 v/v). Dark red solid; Mp 175°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, 2H, J = 7.32 Hz), 7.45-7.37 (m, 3H), 7.17 (d, 1H, J = 4.28 Hz), 6.53 (d, 2H, J = 4.28 Hz), 6.12 (s, 1H); 2.57 (s, 3H), 2.52 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 158.7, 154.5, 143.9, 140.9, 136.0, 133.5, 133.4, 129.2 (t), 128.8, 128.2, 125.1, 122.8, 118.0, 16.9, 16.5, 15.1 ppm; LRMS (EI, 70 EV): 310; HRMS: Calculated for $C_{18}H_{17}BF_2N_2$ 310.1453, found 310.14699.

The compound was also prepared using the general procedure for Suzuki coupling in 65 % yield.

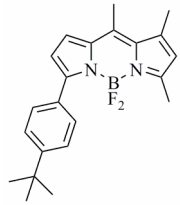
3-(2-thienyl)-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 154e



Obtained according to the general procedure for Stille reaction, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)) in 66% yield. Dark solid; Mp 148°C; ^{1}H-NMR: δ 8.00 (d, 1H, J = 2.73 Hz), 7.37 (d, 1H, J = 5.46 Hz), 7.13-7.09 (m, 2H), 6.67 (d, 1H, J = 3.63 Hz), 6.12 (s, 1H), 2.58 (s, 3H), 2.50 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C-NMR: δ 158.1, 146.8, 143.4, 139.8, 136.3, 134.7, 133.5, 129.5, 129.4, 127.5, 125.2, 122.6, 118.0, 16.8, 16.4, 15.0 ppm; MS (EI, 70 eV) 316; HRMS: Calculated for $C_{16}H_{15}BF_2N_2S$ 316.10171, found 316.10172.

The compound was also prepared using the general procedure for Suzuki coupling in 90 % yield.

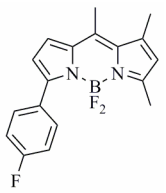
General procedure for Suzuki reaction: 3-(4-*t*-butylphenyl)-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 154b



BODIPY **151b** (53.6 mg, 0.2 mmol) is dissolved in toluene (1ml) and purged with nitrogen. To the solution is added 4-*t*-Butyl-benzeneboronic acid (46 mg, 0.26 mmol, 1.3 equivs.), followed by tetrakis(triphenylphosphine) palladium (22 mg, 0.02 mmol, 10 mol%) and Na_2CO_3 (1 ml of a 1 M aqueous solution). The mixture is refluxed for 3 h, cooled to room temperature and poured in diethyl ether (150 ml). The organic layer is dried over $MgSO_4$, filtered and evaporated to dryness. The crude product is purified by column (Silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield the product as a dark red crystalline solid (68 mg, 93%). Mp 152-154 °C. ^{1}H-

NMR: δ 7.82 (d, 2H, J = 8.22 Hz), 7.45 (d, 2H, J = 8.22 Hz), 7.16 (d, 1H, J = 3.66 Hz), 6.54 (d, 1H, J = 3.66 Hz), 6.10 (s, 1H), 2.53 (s, 6H), 2.38 (s, 3H), 1.35 (s, 9H) ppm; ^{13}C-NMR: δ 158.0, 154.9, 151.8, 143.4, 140.6, 136.1, 133.3, 130.4, 128.9, 125.3, 125.2, 122.5, 118.2, 34.8, 31.4, 16.7, 16.4, 15.0 ppm; LRMS (EI, 70 eV) m/z 366; HRMS: calculated for $C_{22}H_{25}N_2BF_2$ 366.2078, found 366.20892.

3-(*p*-Fluorophenyl)-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 154b

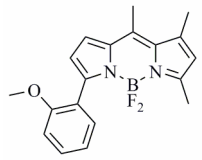


Obtained according to the general procedure for Suzuki coupling, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Orange solid; Mp 150-152°C; ^{1}H-NMR (400 MHz): δ 7.84 (q, 2H, J = 5.49 Hz, J = 8.22 Hz), 7.18 (d, 1H, J = 4.59 Hz), 7.12 (t, 2H, J = 8.22 Hz), 6.49 (d, 1H, J = 3.66 Hz), 6.14 (s, 1H), 2.58 (s, 3H), 2.52 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C-NMR: δ 164.5, 162.0, 159.1, 153.2, 144.2, 140.9, 136.0, 133.6, 131.2(q), 129.6(d), 125.0, 122.9, 117.8, 115.3, 115.1, 16.9, 16.5, 15.1, 15.0 ppm; MS (EI, 70 eV) 328; HRMS: Calculated for $C_{18}H_{16}N_2BF_3$ 328.1359, found 328.13725.

3-(4-Methoxyphenyl)-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 154f

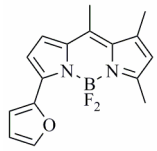
Obtained according to the general procedure for Suzuki coupling, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Red solid; Mp 147°C; ^{1}H-NMR: δ 7.83 (d, 2H, J = 9.12 Hz), 7.18 (d, 1H, J = 3.66 Hz), 6.97 (d, 2H, J = 8.22 Hz), 6.53 (d, 1H, J = 3.63 Hz), 6.11 (s, 1H), 3.85 (s, 3H), 2.57 (s, 3H), 2.42 (s, 3H) ppm; MS (EI, 70 eV) 340; HRMS: Calculated for $C_{19}H_{19}BF_2N_2O$ 340.1559, found 340.1565.

3-(2-Methoxyphenyl)-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



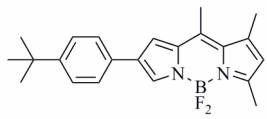
Obtained according to the general procedure for Suzuki coupling, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Purple solid; ^{1}H-NMR: δ 7.68 (d, 1H, J = 7.53 Hz), 7.38 (t, 1H, J = 8.46 Hz), 7.18 (d, 1H, J = 4.14 Hz), 7.05 (t, 1H, J = 6.78 Hz), 6.97 (d, 1H, J = 8.1 Hz), 6.53 (d, 1H, J = 4.14 Hz), 6.08 (s, 1H), 3.79 (s, 3H), 2.57 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 158.2, 157.8, 151.1, 143.5, 140.9, 135.1, 133.4, 131.9, 130.3, 124.5, 122.7, 122.3, 120.1, 119.6, 111.2, 56.0, 16.8, 16.5, 15.0 ppm; LRMS (EI, 70 EV): 340.

3-(2-Furyl)-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 154d



Obtained according to the general procedure for Suzuki coupling, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Red solid; Mp 128°C; ^{1}H-NMR (400 MHz): δ 7.5 (s, 2H), 7.12 (d, 1H, J = 4.56 Hz), 6.87 (d, 1H, J = 3.66 Hz), 6.55 (d, 1H, J = 1.83 Hz), 6.11 (s, 1H), 2.59 (s, 3H), 2.51 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C-NMR: δ 157.7, 146.9, 143.6, 143.5, 143.2, 139.6, 136.1, 133.5, 125.3, 122.4, 116.2, 113.4, 113.3, 113.2, 113.0, 16.7, 14.9 ppm; MS (EI, 70 eV) 300; HRMS: Calculated for $C_{16}H_{15}BF_2N_2O$ 300.12455, found 300.12388.

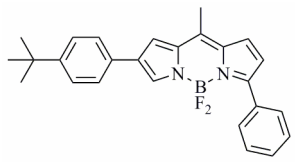
2-(4-*t*-Butylphenyl)-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 155a



Obtained according to the general procedure for Suzuki coupling, but with only 1 mol% of $Pd(PPh_3)_4$. Purified by column chromatography (Silica;

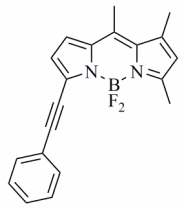
CH_2Cl_2: Petroleum ether (1:1, v/v)) to yield a red solid. Mp 166-168°C; ^{1}H-NMR: δ 7.91 (s, 1H), 7.49 (d, 2H, J = 8.2 Hz), 7.39 (d, 2H, J = 8.2 Hz), 7.26 (s, 1H), 6.15 (s, 1H), 2.58 (s, 6H), 2.42 (s, 3H), 1.34 (s, 9H) ppm; ^{13}C-NMR: δ 160.0, 149.8, 145.2, 141.6, 135.6, 134.9, 134.3, 1341.4, 130.8, 125.7, 125.0, 122.7, 119.2, 34.5, 31.3, 16.9, 16.5, 14.9 ppm; LRMS (EI, 70 eV) m/z 366; HRMS: calculated for $C_{22}H_{25}BF_2N_2$ 366.20789, found 366.20801.

2-(4-*t*-Butylphenyl)-5-phenyl-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 155b



Obtained according to the general procedure for Suzuki coupling, but with only 1 mol% of $Pd(PPh_3)_4$. Purified by column chromatography (Silica; Petroleum ether: EtOAc (7:3, v/v)) to yield a purple solid. Mp 201°C; ^{1}H-NMR: δ 8.06 (s, 1H), 7.93 (m, 2H), 7.50-7.36 (m, 9H), 6.66 (d, 1H, J = 4.56 Hz), 2.63 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C-NMR: δ 159, 150.6, 143.2, 139.7, 137.7, 135.5, 133.4, 1323, 130.2, 129.9, 129.4, 128.8, 128.4, 126.0, 125.2, 120.9, 120.3, 34.7, 31.4, 16.1 ppm.

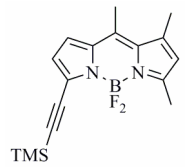
3-Phenylethynyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 156a



BODIPY **151b** (53.6 mg, 0.2 mmol) is dissolved in THF (2ml) and *i*Pr_2NEt (1ml) and purged with nitrogen. To the resulting solution is added phenylacetylene (29 µl, 0.26 mmol, 1.3 equivs.), followed by tetrakis(triphenylphosphine) palladium (22 mg, 0.02 mmol, 10 mol%) and CuI (3.8 mg, 0.02 mmol, 10 mol%). The mixture is refluxed for 3 h and cooled to room temperature after which the solvent is stripped. The product is purified by column (Silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield the desired compound as a purple crystalline solid (31 mg, 46%). Mp 202-204 °C; ^{1}H-NMR: δ 7.61 (d, 2H, J = 3.66 Hz), 7.33 (m, 3H), 7.04 (d, 1H, J = 3.66 Hz), 6.63 (d, 1H, J = 3.66 Hz), 6.18 (s, 1H), 2.62 (s, 3H), 2.53 (s, 3H), 2.41

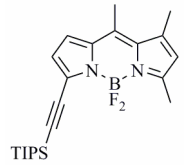
(s, 3H) ppm; ^{13}C-NMR: δ 161.5, 145.7, 139.9, 135.6, 135.4, 132.4, 132.1, 129.5, 128.7, 123.8, 123.6, 123.2, 121.6, 98.3, 83.2, 17.3, 16.7, 15.6 ppm; LRMS (EI, 70 eV) m/z 334; HRMS: calculated for $C_{20}H_{17}BF_2N_2$ 334.1453, found 334.14607.

3-Trimethylsilylethynyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 156b



BODIPY **151b** (53.6 mg, 0.2 mmol) is dissolved in THF (2ml) and *i*Pr$_2$NEt (1ml) and purged with nitrogen. To the resulting solution is added trimethysilylacetylene (37 µl, 0.26 mmol, 1.3 equivs.), followed by tetrakis(triphenylphosphine) palladium (22 mg, 0.02 mmol, 10 mol%) and CuI (3.8 mg, 0.02 mmol, 10 mol%). The mixture is stirred at 80°C in a closed vial for 3 h and cooled to room temperature after which the solvent is stripped. The product is purified by column (Silica, CH_2Cl_2/petroleum ether; 1:1, v/v, second column: Silica; Diethyl ether: Petroleum ether (1:2, v/v)) to yield the desired compound as orange solid (32 mg, 48%). Mp 241-243°C; ^{1}H-NMR: δ 6.97 (d, 1H, J = 3.63 Hz), 6.56 (d, 1H, 3.66 Hz), 6.17 (s, 1H), 2.60 (s, 3H), 2.52 (s, 3H), 2.41 (s, 3H), 0.29 (s, 9H) ppm; ^{13}C-NMR: δ 161.6, 145.5, 139.7, 135.0, 134.7 131.1, 123.5 ,122.7, 121.6, 104.1, 97.1, 16.2, 16.2, 15.1 ppm; LRMS (EI, 70 eV) m/z 330; HRMS: calculated for $C_{17}H_{21}BF_2N_2Si$ 330.15351, found 330.15356.

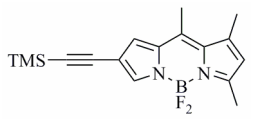
3-Triisopropylsilylethynyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 156b



BODIPY **151b** (414 mg, 1 mmol) is dissolved in dioxane (4 ml) and *N*-Ethyl Morpholine (4 ml) and purged with nitrogen. To the resulting solution is added triisopropylsilylacetylene (185 µl, 1.3 mmol, 1.3 equivs.), followed by tetrakis(triphenylphosphine) palladium (55 mg, 0.05 mmol, 5 mol%) and CuI (19 mg, 0.02 mmol, 10 mol%). The mixture is stirred at 80°C for 10 h and cooled to room temperature after which the solvent is stripped. The product is purified by column (Silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to

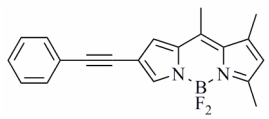
yield **156b** as a shiny red solid (290 mg, 70%). Mp 136 °C; ^{1}H-NMR: 6.97 (d, 1H, J = 3.78 Hz), 6.5 (d, 1H, J = 3.78 Hz), 6.15 (s, 1H), 2.57 (s, 3H), 2.50 (s, 3H), 2.39 (s, 3H), 1.16 (s, 21H) ppm; ^{13}C-NMR: 161.4, 145.3, 139.7, 135.0, 134.8, 131.5, 123.4, 122.8, 121.7, 101.3, 98.9, 18.7, 17.0, 16.3, 15.1, 11.5 ppm; LRMS (EI, 70 eV) m/z 414; HRMS: calculated for $C_{23}H_{33}BF_2N_2Si$ 414.2474, found 414.24666.

2-Trimethylsilylethynyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 158b



2-Iodo-5,7,8-trimethyl BODIPY (53.6 mg, 0.2 mmol) is dissolved in *i*Pr$_2$NH (2ml) and purged with nitrogen. To the resulting solution is added trimethysilylacetylene (37 µl, 0.26 mmol, 1.3 equivs.), followed by tetrakis(triphenylphosphine) palladium (1.1 mg, 0.002 mmol, 0.5 mol%) and CuI (1 mg, 0.005 mmol, 2.5 mol%). The mixture is stirred at 80°C in a closed vial for 2 h and cooled to room temperature. The mixture is poured in diethyl ether (100 ml), and extracted with diluted hydrochloric acid (2 x 100 ml, or until acidic), $NaHCO_3$ (2 x 100 ml, or until basic) and brine (100 ml). The organic layer is collected, dried, after which the solvent is stripped. The product is purified by column (Silica, CH_2Cl_2/ Petroleum ether; 1:1, v/v) to yield the dye as an orange solid. Mp 213-214°C; ^{1}H-NMR: δ 7.68 (s, 1H), 7.11 (s, 1H), 6.20 (s, 1H), 2.57 (s, 3H), 2.51 (s, 3H), 2.42 (s, 3H), 0.23 (s, 9H) ppm; ^{13}C-NMR: δ 162.3, 146.7, 141.6, 140.3, 135.3, 133.3, 125.2, 123.8, 111.1, 98.7, 95.6, 17.1, 16.3, 15.1 ppm; LRMS (EI, 70 eV) m/z 330; HRMS: calculated for $C_{17}H_{21}BF_2N_2Si$ 330.15351, found 330.15341.

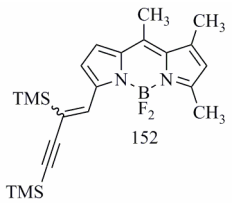
2-Phenylethynyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 158a



2-Iodo-5,7,8-trimethyl BODIPY (53.6 mg, 0.2 mmol) is dissolved in *i*Pr$_2$NH (2ml) and purged with nitrogen. To the resulting solution is added phenylacetylene (29 µl, 0.26 mmol, 1.3 equivs.), followed by tetrakis(triphenylphosphine) palladium (1.1 mg, 0.002 mmol, 0.5 mol%) and CuI (1 mg, 0.005 mmol, 2.5 mol%). The mixture is stirred at 80°C in a closed vial for 90 minutes, and cooled to room temperature. The mixture is

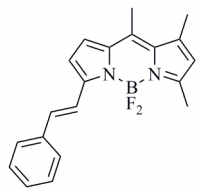
poured in diethyl ether (100 ml), and extracted with diluted hydrochloric acid (2 x 100 ml, or until acidic), $NaHCO_3$ (2 x 100 ml, or until basic) and brine (100 ml). The organic layer is collected, dried, after which the solvent is stripped. The product is purified by column (Silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield the dye as a bright red solid. Mp 191-192°C; ^{1}H-NMR: δ 7.74 (s, 1H), 7.49 (m, 2H), 7.32 (m, 2H), 7.15 (s, 1H), 6.19 (s, 1H), 2.58 (s, 3H), 2.52 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C-NMR: 162.1, 146.7, 141.5, 139.9, 135.2, 133.7, 131.5, 128.4, 128.0, 124.7, 123.7, 123.6, 111.2, 90.4, 83.2, 17.1, 16.4, 15.2 ppm; LRMS (EI, 70 eV) m/z 334; HRMS: calculated for $C_{20}H_{17}BF_2N_2$ 334.14529, found 334.14542.

3-((Z)-(but-3-en-1-yne-1,3-diyl)*bis*(trimethylsilane))-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 157



The compound was isolated from a Sonogashira reaction with TMSA (1.3 eq.), BODIPY **151b**, $Pd(PPh_3)_4$ (10%) and CuI (10%), as a purple film. No crystals obtained; ^{1}H-NMR: δ 7.73 (d, 1H, J = 4.53 Hz), 7.46 (s, 1H), 7.12 (d, 1H, J = 4.71 Hz), 6.14 (s, 1H), 2.58 (s, 3H), 2.55 (s, 3H), 2.42 (s, 3H), 0.26 (s, 9H), 0.25 (s, 9H) ppm; ^{13}C-NMR: δ 160.9, 151.9, 145.9, 141.8, 137.0, 136.9, 136.1, 131.4, 126.5, 124.7, 120.1, 113.1, 108.7, 18.8, 18.4, 17.9 ppm; LRMS (EI, 70 EV): 428; HRMS: Calculated for $C_{22}H_{31}BF_2N_2Si_2$ 428.2087, found 428.20965.

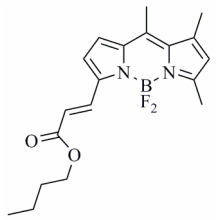
General procedure for Heck-reaction: 3-Styrenyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 159a



BODIPY **151b** (53.6 mg, 0.2 mmol) is dissolved in xylene (2ml) and purged with nitrogen. To the resulting solution is added styrene (30 µl, 0.26 mmol, 1.3 equivs.), followed by $Pd_2(dba)_3$ (18 mg, 0.02 mmol, 10 mol%), tri-(2-furyl)phosphine (4.6 mg, 0.04 mmol, 20 mol%) and Na_2CO_3 (mg, 0.4 mmol, 2 eq.). The mixture is stirred at 130°C in a closed vial for 3 h and cooled to

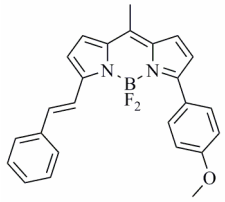
room temperature after which the solvent is stripped. The product is purified by column (Silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield the dye as dark crystals. Mp 240-243°C; ^{1}H-NMR: δ 7.63 (d, 1H, J = 16.3 Hz), 7.57 (d, 2H, J = 7.32 Hz), 7.35 (t, 2H, J = 7.04 Hz), 7.28 (d, 1H, J = 7.32 Hz), 7.28 (s, 1H), 7.13 (d, 1H, J = 4.28 Hz), 6.84 (d, 1H, J = 4.28 Hz), 6.11 (s, 1H), 2.59 (s, 3H), 2. 40 (s, 3H) ppm; ^{13}C-NMR: δ 156.9, 152.3, 142.7, 139.0, 136.8, 135.9, 134.9, 133.3, 129.8, 128.7, 125.7, 121.9, 119.5, 114.5, 16.7, 16.4, 14.9 ppm; MS (EI, 70 eV) 336.

3-(2-(Butoxycarbonyl vinyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 159b



Obtained according to the general procedure for Heck coupling after 4h, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Red solid; Mp 163°C; ^{1}H-NMR: δ 8.04 (d, 1H, J = 15.99 Hz), 7.05 (d, 1H, J = 4.14 Hz), 6.79 (d, 1H, J = 4.32 Hz), 6.44 (d, 1H, J = 16.17 Hz), 6.20 (s, 3H), 4.21 (t, 2H, J = 6.6 Hz), 2.60 (s, 3H), 2.54 (s, 3H), 2.42 (s, 3H), 1.72 (m, 3H), 1.48 (m, 2H), 0.96 (t, 3h, J = 7.35 Hz) ppm; ^{13}C-NMR: δ 166.7, 161.5, 146.5, 145.8, 140.3, 136.5, 134.9, 134.1, 123.8, 121.6, 115.5, 64.6, 30.8, 19.2, 17.0, 16.3, 15.2, 13.9 ppm; MS (EI, 70 eV); HRMS: Calculated for $C_{19}H_{23}BF_2N_2O_2$ 360.18206, found 360.18217.

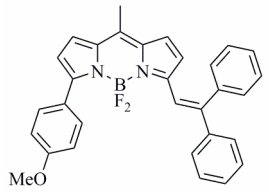
3-(*p*-Anisyl)-5-(2-phenylvinyl)-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene 159c



Obtained according to the general procedure for Heck coupling, after 1h, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Dark shiny solid; Mp 184-186°C; ^{1}H-NMR: δ 7.92 (d, 2H, J = 8.85 Hz), 7.67 (d, 1H, J = 16.38 Hz), 7.57 (d, 2H, J = 7.14 Hz), 7.38-7.21 (m,

6H), 7.02 (d, 2H, J = 8.85 Hz), 6.92 (d, 1H, J = 4.5 Hz), 6.61 (d, 1H, J = 4.14 Hz), 3.88 (s, 3H), 2.56 (s, 3H) ppm; ^{13}C-NMR: δ 160.7, 148.0, 154.9, 138.5, 136.9, 136.4, 131.2, 131.1, 131.0, 129.1, 128.8, 127.7, 127.0, 126.5, 125.4, 119.4, 119.4, 116.2, 113.9, 55.3, 15.5 ppm; MS (EI, 70 eV) ; HRMS: Calculated for $C_{18}H_{17}N_2BF_2$ 310.14529, found 310.14699.

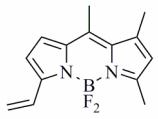
3-(2,2-Diphenylvinyl)-5-(*p*-anisyl)-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 159d



Obtained according to the general procedure for Heck coupling, after 1h, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Dark crystalline solid; Mp 184-185°C; ^{1}H-NMR: δ 7.91 (d, 2H, J = 8.85 Hz), 7.63 (s, 1H), 7.51-7.19 (m, H), 6.99 (d, 2H, J = 8.67 Hz), 6.86 (d, 1H, J = 3.87 Hz), 6.61 (d, 1H, J = 3.93 Hz) ppm; ^{13}C-NMR: δ 160.5, 156.9, 154.1, 149.3, 141.7, 140.3, 138.2, 136.9, 135.5, 132.4, 130.9, 130.2, 130.6, 128.7, 128.5, 128.2, 128.1, 126.3, 125.8, 125.2, 120.1, 119.4, 118.6, 113.7, 55.2, 15.5 ppm; MS (EI, 70 eV) 490; HRMS: Calculated for $C_{31}H_{25}ON_2BF_2$ 490.20280, found 490.20042.

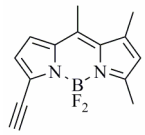
5.3. 3-Ethenyl and 3-ethynyl BODIPY dyes

3-Ethenyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 162b



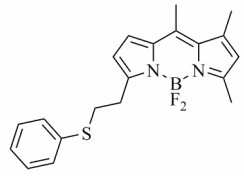
Obtained according to the general procedure for the Stille reaction, but in dioxane rather than toluene, as a brownish red solid; Mp 154°C; ^{1}H-NMR: δ 7.23 (m, 1H), 7.09 (d, 1H, J = 3.96 Hz), 6.70 (d, 1H, J = 4.32 Hz), 6.11 (s, 1H), 5.90 (d, 1H, J = 17.52 Hz), 5.52 (d, 1H, J = 11.1 Hz), 2.56 (s, 3H), 2.52 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C-NMR: δ 128.0, 152.8, 125.1, 122.1, 121.7, 115.3, 113.6, 16.7, 16.3, 14.7 ppm (not all signals fully resolved).

3-Ethynyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 162a



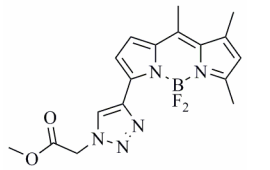
Obtained according to the general procedure for the Stille reaction, but in dioxane rather than toluene, as a red solid; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.98 (d, 1H, J=3.96 Hz), 6.61 (d, 1H, J=3.96 Hz), 6.21 (s, 1H), 3.62 (s, 1H), 2.61 (s, 3H), 2.54 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 162.5, 146.2, 140.1, 134.7, 129.6, 123.9, 122.4, 121.5, 92.2, 84.9, 19.4, 18.7, 16.9 ppm.

3-(2-Phenylsulfanyl-ethyl)-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 163



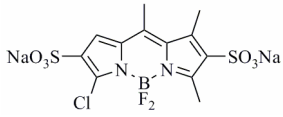
Crude vinyl-BODIPY from a 0.1 mmolar Stille reaction is dissolved in ethanol (5 ml), followed by the addition of thiophenol (10 µl, 0.1 mmole) and K_2CO_3, and stirred overnight at room temperature. The crude mixture is dissolved in diethyl ether, and thoroughly washed with aqueous sodium carbonate. The compound is purified *via* preparative TLC. Orange solid; Mp 82°C; ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.39 (d, 2H, J=7.14 Hz), 7.28 (t, 2H, J=7.74 Hz), 7.17 (t, 1H, J=7.35 Hz), 7.07 (d, 1H, J=4.14 Hz), 6.31 (d, 1H, J=3.96 Hz), 6.12 (s, 1H), 3.30 (m, 4H), 2.55 (s, 3H), 2.52 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$,100 MHz): δ 157.9, 155.0, 143.7, 140.9, 136.4, 134.6, 133.3, 129.6,129.2, 129.0, 127.7, 126.0, 124.2, 122.3, 116.6 ppm; LRMS (EI, 70 EV): 370 ; HRMS: Calculated for $C_{20}H_{21}BF_2N_2S$ 370.1487, found 370.1486.

Click product of 162a and methyl azido acetate; 164



Alkyne BODIPY **162a** (26 mg, 0.1 mmole) is dissolved in THF (1 ml), followed by the addition of methyl azidoacetate (11.5 mg, 0.1 mmole, 1 equiv.) and tetrakis acetonitrile copper hexafluorophosphate (38 mg, 0.1 mmole, 1 equiv.) and the mixture is stirred at reflux for 2 hours, followed by evaporation of the solvent. The crude solid is purified chromatographically (Silica; DCM / EtOAc; 9:1 v/v) to yield the product as a red crystalline solid; Mp 230°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.56 (s, 1H), 7.28 (d, 1H, J = 4.28 Hz), 7.21 (d, 1H, J = 4.28 Hz), 6.16 (s, 1H), 5.23 (s, 2H), 3.81 (s, 3H), 2.58 (s, 6H), 2.43 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 166.6, 158.6, 144.1, 143.7, 140.7, 136.1, 133.7, 125.7, 125.5, 125.4, 122.8, 11.6, 117.3, 53.2, 50.9, 16.9, 16.6, 15.0 ppm; LRMS (EI, 70 EV): 373; HRMS: Calculated for $C_{17}H_{18}BF_2N_5O_2$ 373.1522, found 373.15028.

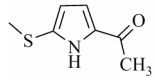
2,6-bis(natriumsulfonato)-3-Chloro-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 162



BODIPY **151b** (536 mg, 0.2 mmole) is suspended in dichloromethane (5 ml) at -78°C. Chlorosulfonic acid (27 µl, 0.4 mmole, 2 equivs.) is added and the solution is brought to 0°C, where it is stirred for 20 minutes. An aqueous solution of Na_2CO_3 (0.4 mmole in 2 ml of H_2O) is added, followed by evaporation of the solvents. The crude solid is purified through column chromatography (Silica, DCM/Methanol; (8:2 v/v)), followed by partial evaporation and lyophilization to yield the dye as an orange solid (61%). Mp >300°C; ^{1}H-NMR (D_2O, 400 MHz): δ 7.44 (s, 1H), 2.59 (s, 6H), 2.43 (s, 3H) ppm; ^{13}C-NMR (D_2O, 100 MHz): δ 160.4, 146.8, 146.2, 141.6, 134.3, 133.4, 131.1, 129.9, 123.9, 16.4, 14.6, 13.9 ppm.

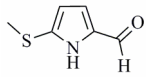
5.4. Sulfur substituted BODIPY dyes

2-Methylsulfanyl-5-acetylpyrrole 171b



Methylsulfanylpyrrole is prepared from 10 mmole of pyrrole through thiocyanation, followed by reaction with methylmagnesium chloride. The product thus obtained is used directly in the Vilsmeier acylation. To a solution of 2-methylsulfanyl pyrrole in dichloromethane (50 ml), is added preformed Vilsmeier reagent (from 10 mmole of DMA and 10 mmole of $POCl_3$) at 0°C. The resulting solution soon darkens, and is stirred at room temperature for 3 hours, followed by quenching with an aqueous Na_2CO_3 solution (50 mmole of carbonate in 100 ml of water). The mixture is refluxed for one hour, cooled, extracted with diethyl ether, and the organic layer is collected in a standard workup procedure. The crude product is purified chromatographically (Silica, DCM) to yield colourless crystals (19% from pyrrole). Mp 60°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.82 (s, Br, 1H, NH), 6.87 (q, 1H, J = 2.41 Hz, J = 3.75 Hz), 6.24 (q, 1H, J = 2.64 Hz, J = 3.78 Hz), 2.46 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 187.0, 133.2, 132.5, 118.0,113.3, 24.19, 18.64 ppm; MS (CI): 156.

2-Methylsulfanyl-5-formylpyrrole 171a



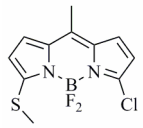
Prepared according to the procedure mentioned hereabove, as white crystals. Mp 103-104°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.2 (s, br, 1H, NH), 9.37 (s, 1H), 6.95 (q, 1H, J = 2.25 Hz), J = 3.78 Hz), 6.28 (q, 1H, J = 2.07 Hz, J = 3.6 Hz), 2.51 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 177.9, 135.9, 133.7, 122.9, 112.9, 17.8 ppm; LRMS (EI, 70 EV): 141.

3-Methylsulfanyl-5,7,8-trimethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 172a

Obtained according to the general condensation procedure as reddish brown crystals. Mp 203°C; ^{1}H-NMR: δ 7.12 (d, 1H, J = 3.96 Hz), 6.32 (d, 1H, J = 3.96 Hz), 3.08 (s, 1H), 2.57 (s, 3H), 2.54 (s, 3H), 2.47 (s, 3H), 2.37 (s, 3H)

ppm; ^{13}C-NMR: δ 156.3, 153.9, 142.2, 137.9, 134.8, 132.8, 125.6, 121.6, 114.1, 41.3, 16.5, 16.1, 15.6 ppm; LRMS (EI, 70 EV): 280; HRMS: Calculated for $C_{13}H_{15}BF_2N_2S$ 280.1017, found 280.1029.

3-Methylsulfanyl-5-chloro-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 173a

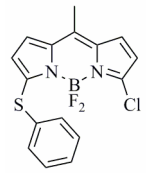


Obtained according to the general condensation procedure as golden crystals. Mp 223°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.28 (d, 1H, J = 4.52 Hz), 7.00 (d, 1H, J = 3.8 Hz), 6.48 (d, 1H, J = 4.52 Hz), 6.31 (d, 1H, J = 4.04 Hz), 2.62 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 162.4, 138.7, 137.4, 133.6, 129.3, 124.4, 121.7, 117.2, 116.1, 15.5, 14.9 ppm; LRMS (EI, 70 EV): 286; HRMS: Calculated for $C_{11}H_{10}BClF_2N_2S$ 286.0314, found 286.03117.

3-Octylsulfanyl-5-chloro-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 173c

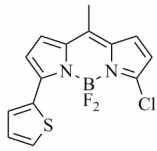
Obtained according to the general condensation procedure as a bordeaux solid with golden luster. Mp 121-123°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, 1H, J = 5.19 Hz), 6.99 (d, 1H, J = 3.78 Hz), 6.50 (d, 1H, J = 4.53 Hz), 6.31 (d, 1H, J = 3.96 Hz), 3.08 (t, 2H, J = 7.35 Hz), 2.44 (s, 3H), 1.79 (m, 2H), 1.45 (m, 2H), 1.28 (m, 2H), 0.87 (m, 5H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 162.2, 138.4, 137.2, 136.8, 133.5, 129.3, 124.1, 117.7, 115.9, 32.8, 31.8, 29.2, 29.2, 29.1, 28.9, 22.7, 14.9, 14.2 ppm; LRMS (EI, 70 EV): 384; HRMS: Calculated for $C_{18}H_{24}BClF_2N_2S$ 384.1410, found 384.14102.

3-Phenylsulfanyl-5-chloro-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 173b



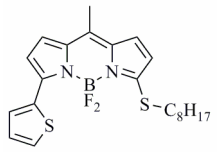
Obtained according to the general condensation procedure as a deep red solid with golden luster; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.68 (m, 2H), 7.47 (m; 3H), 7.11 (d, 1H, J = 4.35 Hz), 7.02 (d, 1H, J = 3.81 Hz), 6.34 (d, 1H, J = 3.96 Hz), 5.88 (d, 1H, J = 4.5 Hz), 2.43 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 162.1, 138.8, 136.8, 137.5, 135.4, 133.6, 130.3, 129.0, 128.8, 124.5, 119.4, 116.1, 14.9 ppm; LRMS (EI, 70 EV): 348; HRMS: Calculated for $C_{16}H_{12}BClF_2N_2S$ 348.0471, found 348.0471.

3-(2-Thienyl)-5-chloro-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 174



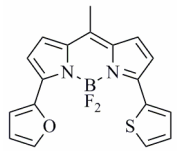
Liebeskind reaction: BODIPY (27 mg, 0.1 mmole) is dissolved in dioxane (1 ml), followed by the addition of thiophene-2-boronic acid (17 mg, mmole, 1.3 equiv.), $Pd(PPh_3)_4$ (11 mg, 10 mol%) and CuTC (24.5 mg, 0.14 mmole, 1.4 equiv.). The solution is purged with nitrogen, and the mixture is stirred in a closed vessel at 100°C for 2 hours. The solvent is stripped *in vacuo*, and the crude product is purified chromatographically (Silica, petroleum ether/ diethyl ether 2:1 (v/v)) to yield the dye as a metallic purple solid. Mp 170°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.21 (d, 1H, J = 3.75 Hz), 7.53 (d, 1H, J = 5.1 Hz), 7.30 (d, 1H, J = 4.53 Hz), 7.18 (t, 1H, J = 3.96 Hz), 7..10 (d, 1H, J = 3.96 Hz), 6.84(d, 1H, J = 4.32 Hz), 6.39 (d, 1H, J = 5.13 Hz), 2.52 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 152.2, 140.3, 139.6, 137.5, 133.7, 133.4, 132.1, 132.0, 131.9, 130.1, 129.2, 129.2, 129.0, 128.3, 125.3, 120.9, 116.9, 15.3 ppm; LRMS (EI, 70 EV): 322; HRMS: Calculated for $C_{14}H_{10}BClF_2N_2S$: 322.0314, found 322.03292.

3-(2-Thienyl)-5-octylsulfanyl-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



3-octylsylfanyl-5-chloro BODIPY (38 mg, 0.1 mmole) is dissolved in dioxane (1 ml), followed by the addition of 2-(tributyltin) thiophene (48 mg, mmole, 1.3 equiv.) and $Pd(PPh_3)_4$ (11 mg, 10 mol%). The solution is purged with nitrogen, and the mixture is stirred in a closed vessel at 100°C for 4 hours. The solvent is stripped *in vacuo*, and the crude product is purified chromatographically (Silica, petroleum ether/ diethyl ether 2:1 (v/v)) to yield the dye as a dark blue solid. ^{1}H-NMR: δ 8.07 (d, 1H, J = 3.78 Hz), 7.65 (d, 1H, J = 4.68 Hz),7.39 (d, 1H, J = 5.07 Hz), 7.19 (d, 1H, J = 4.14 Hz), 7.13-7.08 (m, 1H), 6.72 (d, 1H, J = 4.35 Hz), 6.44 (d, 1H, J = 4.53 Hz), 3.06 (t, 2H, J = 7.53 Hz), 2.47 (s, 3H), 1.78 (m, 2H) ppm; ^{13}C-NMR: δ 158.4, 147.8, 136.6, 136.5, 136.0, 135.1, 134.3, 130.5, 130.1, 130.0, 129.9, 128.8, 127.8, 127.2, 125.4, 118.8, 116.6, 32.7, 31.7, 29.1, 29.0, 28.9, 28.8, 27.2, 22.6, 15.2, 14.0, 13.6, 10.7 ppm; LRMS (EI, 70 EV): 432; HRMS: Calculated for $C_{22}H_{27}BF_2N_2S_2$ 432.1677, found 432.16785.

3-(2-Thienyl)-5-(2-furyl)-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 176



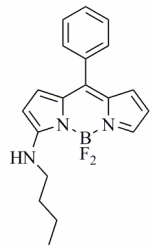
Obtained from a Liebeskind reaction with 2-(tributyltin) furan as a blue solid. Mp 158°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.15 (d, 1H, J = 3.39 Hz), 7.69 (s, 1H), 7.57 (s, 1H), 7.46 (d, 1H, J = 4.53 Hz), 7.23-7.16 (m, 3H), 6.80 (d, 1H, J = 4.14 Hz), 6.60 (m, 1H), 2.55 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 149.2, 146.4, 145.9, 144.5, 138.2, 137.0, 136.9, 134.3, 130.6, 130.5, 128.8, 128.7, 126.8, 126.5, 119.9, 118.3, 115.6, 115.5, 113.4, 15.7 ppm; LRMS (EI, 70 EV): 354; HRMS: Calculated for $C_{18}H_{13}BF_2N_2OS$ 354.0810, found 354.08097.

5.5. Direct substitution of hydrogen

Oxidative subsitution: General procedure for amine substitution

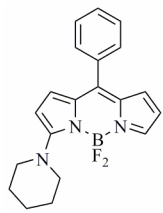
To a solution of BODIPY (0.5 mmol, 134 mg) in DMF (5ml) is added the corresponding amine (1.1 mmol, 2.2 equiv.), the mixture is flushed with oxygen and stirred at room temperature for the indicated time (Table 22) under an oxygen atmosphere. Subsequently, the solution is poured in diethyl ether (100 ml), washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product is purified by filtration over a silica pad with dichloromethane.

3-(*N*-Butylamino)-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 205a



Obtained according to the general procedure for oxidative hydrogen substitution with nitrogen nucleophiles, after overnight stirring. Red crystals; Mp 120°C; ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.47 (m, 6H), 6.93 (d, 1H, J = 5.49 Hz), 6.42 (d, 1H, J = 2.73 Hz), 6.33 (d, 1H, J = 1.83 Hz), 6.32 (s, br, 1H, NH), 6.18 (d, 1H, J = 4.56 Hz), 3.41 (q, 2H, J = 6.39 Hz, J = 13.68 Hz), 1.73 (m, 2H), 1.46 (m, 2H), 0.97 (t, 3H, J = 9.72 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 161.9, 136.2, 134.7, 133.5, 132.8, 132.6, 130.9, 130.4, 129.1, 128.2, 119.8, 113.4, 110.4, 44.5, 32.2, 19.8, 13.7 ppm; LRMS (EI, 70 EV): 339; HRMS: Calculated for $C_{19}H_{20}N_3BF_2$ 339.17183, found 339.17353.

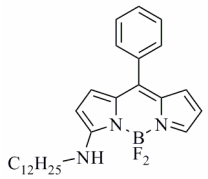
3-(*N*-Piperidinyl)-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 205c



Obtained according to the general procedure for oxidative hydrogen substitution with nitrogen nucleophiles, after overnight stirring. Red crystals;

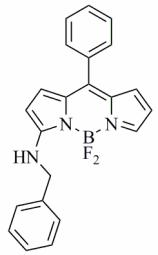
Mp 55°C; ^{1}H-NMR: δ 7.44 (m, 6H), 6.86 (d, 1H, J = 5.46 Hz), 6.32 (s, 2H), 6.26 (d, 1H, J = 5.49 Hz), 3.90 (d, 4H, J = 4.56 Hz), 1.78 (m, 6H) ppm; ^{13}C-NMR: δ 162.1, 135.7, 135.6, 1354.1, 131.9, 131.5, 130.7, 130.5, 128.9, 128.1, 117.9, 113.9, 51.9, 26.5, 24.8 ppm; LRMS (EI, 70 EV): 351; HRMS: Calculated for $C_{20}H_{20}N_3BF_2$ 351.17183, found 351.17179.

3-(*N*-Dodecylamino)-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 205b



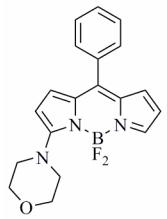
Obtained according to the general procedure for oxidative hydrogen substitution with nitrogen nucleophiles, after overnight stirring. Red oil; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.46 (m, 6H), 6.93 (d, 1H, J = 4.56 Hz), 6.41 (m, 1H), 6.33 (m, 1H), 6.28 (s, br, 1H, NH), 6.18 (d, 1H, J = 5.49 Hz), 3.39 (q, 2H, J = 6.39 Hz, J = 12.78 Hz), 1.69 (m, 2H), 1.26 (m, 18 H), 0.87 (t, 3H, J = 7.32 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 161.9, 136.2, 134.8, 133.5, 132.8, 131.0, 130.4, 129.2, 128.3, 119.9, 113.5, 110.4, 44.9, 32.0, 30.2, 29.7, 29.6, 29.5, 29.4, 29.3, 26.7, 22.8, 14.2 ppm; LRMS (EI, 70 EV): 451; HRMS: Calculated for $C_{27}H_{36}N_3BF_2$ 451.2970, found 451.29731.

3-(*N*-Benzylamino)-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 203e



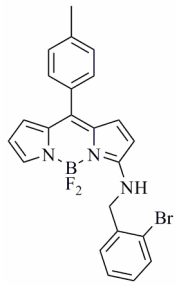
Obtained according to the general procedure for oxidative hydrogen substitution with nitrogen nucleophiles, after overnight stirring. Red solid; Mp 156°C; ^{1}H-NMR: δ 7.88 (d, 1H, J = 8.22 Hz), 7.43 (m, 10H), 6.9 (d, 1H, J = 4.56 Hz), 6.66 (s, br, 1H, NH), 6.34 (m, 1H), 6.13 (d, 1H, J = 4.6 Hz), 4.61 (d, 1H, J = 6.39 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 161.9, 136.7, 136.2, 134.6, 133.9, 133.4, 132.7, 131.7, 130.4, 129.8, 129.3, 129.1, 128.2, 126.9, 120.6, 113.8, 110.3, 48.3 ppm; LRMS (EI, 70 EV): 373; HRMS: Calculated for $C_{22}H_{18}N_3BF_2$ 373.1561, found 373.15777.

3-(*N*-Morpholino)-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 205d



Obtained according to the general procedure for oxidative hydrogen substitution with nitrogen nucleophiles, after overnight stirring. Red solid; Mp 122-123°C; ^{1}H-NMR: δ 7.44 (m, 6H), 6.88 (d, 1H, J = 3.75 Hz), 6.39 (d, 1H, J = 2.46 Hz), 6.35 (m, 1H), 6.20 (d, 1H, J = 3.78 Hz), 3.95 (d, 4H, J = 3.12 Hz), 3.87 (t, 4H, J = 3.21 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 162.2, 151.6, 135.8, 135.0, 133.5, 131.8, 130.5, 129.1, 128.2, 125.6, 113.9, 112.8, 66.8, 50.6 ppm; LRMS (EI, 70 EV): 353; HRMS: Calculated for $C_{19}H_{18}N_3OBF_2$ 353.1511, found 353.15316.

3-(*N*-*o*-Bromobenzylamine)-8-tolyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene

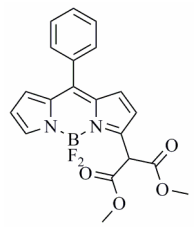


Obtained according to the general procedure for oxidative hydrogen substitution with nitrogen nucleophiles but triethylamine as base, after overnight stirring. Orange solid; Mp 197°C; ^{1}H-NMR: δ 7.58 d, 1H, J = 7.71 Hz), 7.29 (m, 8H), 6.91 (d, 1H, J = 4.89 Hz), 6.72 (s, br, 1H, NH), 6.48 (d, 1H, J = 3.39 Hz), 6.34 (d, 1H, J = 2.28 Hz), 6.10 (d, 1H, J = 4.89 Hz), 4.65 (d, 2H, J = 6.45 Hz), 2.42 (s, 3H) ppm; ^{13}C-NMR: δ 161.5, 139.3, 136.1, 135.9, 134.4, 133.1, 132.7, 131.6, 130.2, 129.5, 128.9, 128.4, 128.0, 122.8, 120.8, 113.7, 109.7, 48.3, 22.6 ppm; LRMS (EI, 70 EV): 451.

Oxidative substitution: General procedure for oxidative hydrogen substitution with carbon nucleophiles,

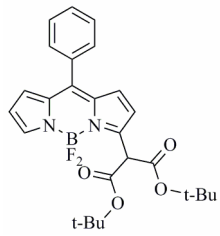
To a solution of 8-phenyl-BODIPY (0.5 mmol, 134 mg) in DMF (5ml) is added the corresponding carbon nucleophile (0.55 mmol, 1.1 equiv.), followed by base (1 mmol, 106 mg, 2 eq.). The mixture is flushed with oxygen and stirred at room temperature for the indicated time under an oxygen atmosphere. Subsequently, the solution is poured in diethyl ether (100 ml), washed with diluted aqueous HCl and brine, dried over MgSO4, filtered and evaporated to dryness. The crude product is purified by column chromatography.

Dimethyl 2-(8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) malonate 205f



Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with Na_2CO_3 or K_2CO_3 as base, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Orange solid; Mp 138°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 1H), 7.58-7.48 (m, 5H), 6.92 (d, 1H, J = 4.28 Hz), 6.88 (d, 1H, J = 4 Hz), 6.68 (d, 1H, J = 4.28 Hz), 6.52 (m, 1H), 5.52 (s, 1H), 3.81 (s, 6H) ppm; ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 166.7, 150.5, 147.1, 144.1, 134.9, 133.5, 131.8, 131.5, 130.7, 130.4, 128.4, 119.5, 118.8, 53.3, 51.8 ppm; LRMS (EI, 70 EV): 398; HRMS: Calculated for $C_{20}H_{17}N_2O_4BF_2$ 398.1249, found 398.12325.

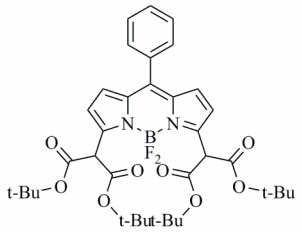
Di-*t*-butyl 2-(8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) malonate 205g



Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with

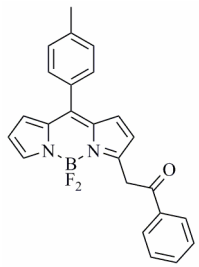
Na_2CO_3 or K_2CO_3 as base, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Orange solid; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.86 (s, 1H), 7.58-7.48 (m, 5H), 6.92 (d, 1H, J = 4.28 Hz), 6.85 (d, 1H, J = 3.76 Hz), 6.70 (d, 1H, J = 4.52 Hz), 6.50 (d, 1H, J = 2.52 Hz), 5.30 (s, 1H), 1.50 (s, 18H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 165.5, 153.0, 146.6, 143.2, 135.2, 134.7, 133.9, 132.1, 130.8, 130.7, 130.5, 128.5, 119.9, 118.3, 82.9, 54.6, 27.9 ppm; LRMS (EI, 70 EV): 482.

3,5-*Bis*-(di-*t*-butylmalon-2-yl)-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 205h



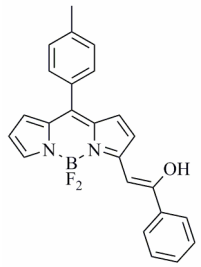
Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with Na_2CO_3 or K_2CO_3 as base, purified by column chromatography (Silica; CH_2Cl_2). Orange solid; Mp 178°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.53 (m, 5H), 6.84 (d, 2H, J = 4.14 Hz), 6.67 (d, 2H, J = 4.14 Hz), 1.49 (s, 36H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 165.5, 151.9, 145.8, 134.7, 133.8, 131.2, 130.5, 128.4, 119.6, 82.8, 54.4, 27.9 ppm; LRMS (EI, 70 EV): 696 ; HRMS: Calculated for $C_{37}H_{47}BF_2N_2O_8$ 696.3394, found 696.3394.

3-(Phenacyl)-8-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 205i



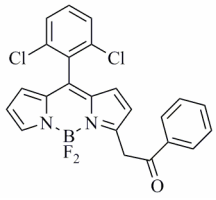
To a solution of 8-tolyl-BODIPY (0.5 mmol, 141 mg) in DMF (5ml) is added acetophenone (66 mg, 0.55 mmol, 1.1 equiv.) followed by potassium *bis*(trimethylsilyl)amide (KHMDS, 1 mmol, 200 mg, 2 eq.). The mixture is flushed with oxygen and stirred at room temperature for 6h under an oxygen atmosphere. Subsequently, the dark solution is poured in diethyl ether (100 ml), washed with diluted aqueous HCl and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product is purified by column

chromatography (silica, CH_2Cl_2). Orange solid; Mp 95°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, 2H, J = 7.32 Hz), 7.99 (s, 1H), 7.61-7.44 (m, 5H), 7.31 (d, 2H, J = 7.74 Hz), 6.94 (d, 1H, J = 3.9 Hz), 6.86 (d, 1H, J = 3.39 Hz), 6.51 (m, 2H), 4.70 (s, 2H), 2.46 (s, 3H) ppm; ^{1}H-NMR (CD_3CN, 600 MHz): 8.05 (d, 2H, J = 7.14 Hz), 7.83 (s, 1H), 7.66 (t, 1H, J = 7.56 Hz), 7.55 (t, 2H, J = 7.5 Hz), 7.51 (d, 2H, J = 8.28 Hz), 7.38 (d, 2H, J = 7.56 Hz), 7.01 (d, 1H, J = 3.78 Hz), 6.90 (d, 1H, J = 3.36 Hz), 6.56 (m, 2H), 4.75 (s, 2H), 2.45 (s, 3H) ppm; ^{13}C-NMR (CD_3CN, 100 MHz): δ 195.7, 157.2, 147.2, 142.6, 142.4, 137.4, 136.0, 134.9, 134.4, 133.4, 133.2 ,131.6, 131.5, 131.0, 130.0, 129.7, 129.1, 122.5, 118.8, 39.7, 21.3 ppm; LRMS (EI, 70 EV): 400; HRMS: Calculated for $C_{24}H_{19}BF_2N_2O$ 400.1559, found 400.15606.



To an NMR-tube filled with a CD_3CN solution of 3-acetophenone BODIPY, was added DBU (approx. 1 eq.). An immediate colour shift from bright orange to deep purple is observed. NMR-analysis shows full conversion to the enol-tautomer. ^{1}H-NMR (CD_3CN, 600 MHz): 7.89 (m, 2H), 7.81 (d, 1H, J = 5.16 Hz), 7.43 (m, 3H), 7.40 (d, 2H, J = 7.32 Hz), 7.27 (d, 2H, J = 7.38 Hz), 7.11 (s, 1H), 6.74 (d, 1H, J = 5.16 Hz), 6.66 (s, 1H), 6.16 (d, 1H, J = 2.22 Hz), 6.04 (d, 1H, J = 2.16 Hz), 2.40 (s, 3H, CH_3) ppm; ^{13}C-NMR (CD_3CN, 150 MHz): δ 185.6, 166.9, 144.0, 138.9, 1138.5, 135.0 134.2, 133.2, 132.0, 131.2, 130.7, 129.6, 129.0, 127.7, 126.7, 126.0, 121.0, 112.2, 111.7, 92.9, 21.2 ppm.

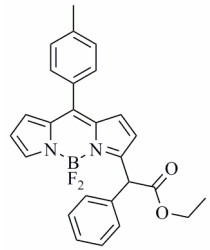
3-(Phenacyl)-8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with KO*t*Bu as base, purified by column chromatography (Silica; CH_2Cl_2). Orange solid; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, 2H, J = Hz), 7.83 (m, 1H), 7.60 (t, 1H, J = Hz), 7.52-7.45 (m, 4H), 7.40(m, 1H), 6.68 (d, 1H, J =

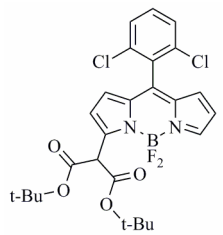
4.04 Hz), 6.61 (d, 1H, J = 3.28 Hz), 6.55 (d, 1H, J = 4.04 Hz), 6.47 (s, 1H), 4.77 (s, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 194.7, 157.5, 143.3, 139.2, 136.5, 135.4, 134.0, 133.8, 131.4, 131.3, 131.0, 128.9, 128.8, 128.5, 128.3, 121.6, 118.4 ppm.

Ethyl (8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) phenylacetate 205j



To a solution of tolyl BODIPY (0.5 mmol, 134 mg) in DMF (5ml) is added ethyl phenylacetate (90 mg, 1.1 equiv.) followed by KO*t*Bu (1 mmol, 112 mg, 2 eq.). The mixture is flushed with oxygen and stirred at room temperature for 6h under an oxygen atmosphere. Subsequently, the dark solution is poured in diethyl ether (100 ml), washed with diluted aqueous HCl and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product is purified by column chromatography (silica, CH_2Cl_2). Orange semisolid at rt; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.84 (s, 1H), 7.47-7.28 (m, 9H), 6.88-6.84 (m, 2H), 6.54 (d, 1H, J = 4.5 Hz), 6.50 (m, 1H), 5.76 (s, 1H), 4.33-4.15 (m, 2H), 2.44 (s, 3H), 1.27 (t, 3H, J = 7.14 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.6, 158.2, 146.9, 142.4, 141.1, 136.5, 135.2, 134.5, 132.1, 131.1, 130.9, 130.6, 130.3, 129.2, 129.0, 128.7, 127.9, 120.0, 117.9, 61.8, 51.1, 23.5, 14.1 ppm; LRMS (EI, 70 EV): 444; HRMS: Calculated for $C_{26}H_{23}BF_2N_2O_2$ 444.1821, found 444.1772.

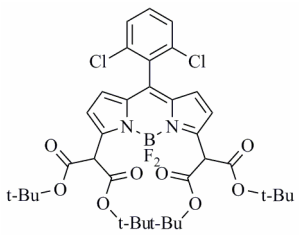
Di-*t*-butyl 2-(8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) malonate



Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with Na_2CO_3 or K_2CO_3 as base, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Orange solid; Mp 168-170°C; ^{1}H-NMR

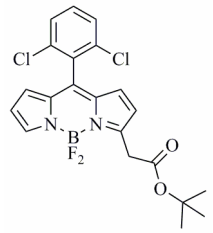
($CDCl_3$, 300 MHz): δ 7.77 (s, 1H), 7.43 (m, 3H), 6.62 (m, 3H), 6.64 (s, 1H), 5.23 (s, 2H), 1.40 (s, 18 H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 166.3, 165.1, 154.4, 144.3, 139.8, 135.3, 135.0, 134.3, 131.3, 130.5, 129.1, 28.3, 120.5, 118.3, 120.5, 118.8, 83.1, 44.4, 28.0 ppm; LRMS (EI, 70 EV): 374(M-*t*Bu_4-2F; 100%), 550 (M, 3%); HRMS: Calculated for $C_{26}H_{27}BCl_2F_2N_2O_4$ 550.1409, found 550.14226.

3,5-*bis*-(di-*t*-butylmalon-2-yl)-8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with Na_2CO_3 or K_2CO_3 as base, purified by column chromatography (Silica; CH_2Cl_2: Petroleum ether (1:1, v/v)). Orange solid; Mp 204°C; ^{1}H-NMR: δ 7.44 (m, 3H), 6.87 (d, 2H, J = 4.32 Hz), 6.60 (d, 2H, J = 4.35 Hz), 5.28 (d, 2H), 1.48 (s, 36H) ppm; ^{13}C-NMR: δ 165.2, 153.1, 138.9, 1354, 134.4, 131.3, 131.2, 129.9, 129.4, 128.2, 127.9, 120.1, 82.9, 54.6, 27.9 ppm.

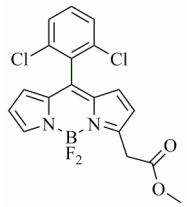
***t*-butyl (8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) acetate 214b**



To a solution of 8-(2,6-dichlorophenyl-BODIPY (0.5 mmol, 204 mg) in DMF (5ml) is added *t*-butyl bromoacetate (102 mg, 1.1 equiv.), followed by KO*t*Bu (1 mmol, 112 mg, 2 eq.). The mixture is flushed with nitrogen and stirred at room temperature for 1h. Subsequently, the dark solution is poured in diethyl ether (100 ml), washed with diluted aqueous HCl and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product is purified by column chromatography (silica, CH_2Cl_2: Petroleum ether (1:1, v/v)). Orange solid; Mp 112°C; ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.82 (m, 1H), 7.46 (d, 2H, J = 7.8 Hz), 7.39 (t, 1H, J = 7.32 Hz), 6.67 (d, 1H, J = 4.26 Hz), 6.58 (m, 2H), 6.45 (d, 1H, J = 2.34 Hz), 4.05 (s, 2H), 1.49 (s, 9H) ppm;

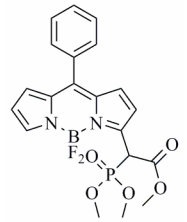
^{13}C-NMR ($CDCl_3$, 150 MHz): δ 167.8, 157.2, 143.3, 239.4, 135.3, 134.2, 133.9, 131.4, 131.2, 130.9, 128.3, 121.3, 118.3, 82.0, 36.1, 28.1 ppm; LRMS (EI, 70 EV): 349 (M-*t*Bu-F); HRMS: Calculated for $C_{21}H_{19}BCl_2F_2N_2O_2$ 450.0885, found 450.08595.

Methyl (8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) acetate 214a



To a solution of 8-(2,6-dichlorophenyl-BODIPY (0.5 mmol, 204 mg) in DMF (5ml) is added methyl bromoacetate (83 mg, 1.1 equiv.), followed by KO*t*Bu (1 mmol, 112 mg, 2 eq.). The mixture is flushed with nitrogen and stirred at room temperature for 1h. Subsequently, the dark solution is poured in diethyl ether (100 ml), washed with diluted aqueous HCl and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product is purified by column chromatography (silica, CH_2Cl_2: Petroleum ether (1:1, v/v)). Orange solid; Mp 52°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.85 (s, 1H), 7.49-7.38 (m, 3H), 6.68 (d, 1H, J = 4.14 Hz), 6.61 (m, 2H), 6.48 (s, 1H), 4.14 (s, 2H), 3.78 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 169.3, 155.8, 143.9, 139.4, 135.3, 135.1, 134.1, 131.3, 130.8, 128.8, 128.3, 121.0, 118.0, 52.6, 34.6 ppm; LRMS (EI, 70 EV): 408; HRMS: Calculated for $C_{18}H_{13}BCl_2F_2N_2O_2$ 408.0415, found 408.03931.

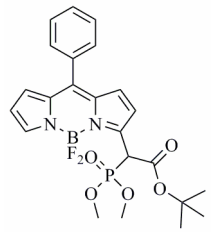
Trimethyl (8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) phosphonoacetate 219a



Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with KO*t*Bu as base, purified by column chromatography (silica, CH_2Cl_2: Ethyl acetate (9:1, v/v)). Orange solid; Mp 135-137°C; ^{1}H-NMR: δ 7.88 (s, 3H), 7.54 (m, 5H), 6.95 (m, 2H), 6.89 (d, 1H, J = 3.78 Hz), 6.53 (d, 1H, J = 2.46 Hz) 5.24 (d, 1H, J = 24.66 Hz), 3.82 (m, 9 H) ppm; ^{13}C-NMR: δ 165.9 (d),

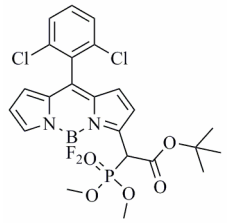
149.5, 146.7, 143.5, 134.9, 134.6, 133.5, 131.9, 131.2, 130.7, 130.4, 128.4, 121.2, 118.5, 54.2 (dd), 46.4, 44.7 ppm; LRMS (EI, 70 EV): 448; HRMS: Calculated for $C_{20}H_{20}BF_2N_2O_5P$ 448.1171, found 448.1183.

Dimethyl *t*-butyl (8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) phosphonoacetate 219b



Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with KO*t*Bu as base, purified by column chromatography (silica, CH_2Cl_2: Ethyl acetate (9:1, v/v)). Orange solid; Mp 95°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 1H), 7.55 (m, 5H), 6.99 (d, 1H, J = 4.04 Hz), 6.94 (d, 1H, J = 4.52 Hz), 6.88 (d, 1H, J = 3.76 Hz), 6.54 (s, 1H), 5.18 (d, 1H, J = 24.68 Hz), 3.89 (d, 3H, J = 11.04 Hz)), 3.78 (d; 3H, J = 11.08 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 164.1 (d), 151.0, 146.6, 143.1, 134.1, 134.6, 133.8, 132.0, 130.8, 130.7, 130.6, 128.5, 125.0, 121.7, 118.3, 83.6, 54.1 (dd), 47.5, 46.2, 29.8, 27.9 ppm; LRMS (EI, 70 EV): 370 (M-*t*Bu; 100%), 490 (M, 17%); HRMS: Calculated for $C_{23}H_{26}BF_2N_2O_5P$ 490.1640, found 490.1643.

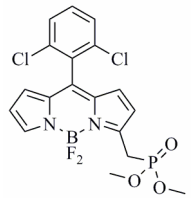
Dimethyl *t*-butyl (8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacen-3-yl) phosphonoacetate 219c



Obtained according to the general procedure for oxidative hydrogen substitution with carbon nucleophiles, after overnight stirring and with KO*t*Bu as base, purified by column chromatography (silica, CH_2Cl_2: Ethyl Acetate (9:1, v/v)). Orange solid; Mp 57°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.85 (s, 1H), 7.45 (m, 3H), 6.94 (d, 1H, J = 4.28 Hz), 6.69 (d, 1H, J = 4.28 Hz), 6.63 (d, 1H, J = 4 Hz), 6.48 (d, 1H, J = 2.8 Hz), 5.15 (d, 1H, J = 24.92 Hz), 3.88 (d, 3 H, J = 11.04 Hz), 3.71 (d, 3 H, J = 11.08 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 163.8 (d), 152.4, 144.1, 139.7, 135.3, 134.1, 134.9, 134.2, 131.3, 131.2, 130.3, 129.0, 128.3, 128.2, 122.3, 1187, 83.6, 60.4, 54.0

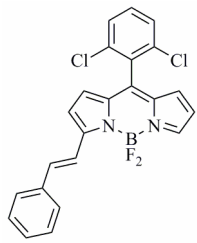
(dd), 47.7, 46.4, 27.9 ppm; LRMS (EI, 70 EV): 438 (M-*t*Bu; 100%), 558 (M, 4%); HRMS: Calculated for $C_{23}H_{24}BCl_2F_2N_2O_5P$ 558.0861, found 558.08329.

3-(dimethylphosphonomethyl)-8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 220



3-(dimethylphosphono-*t*-butylacetate)-BODIPY (558 mg, 1 mmole) is dissolved in CH_2Cl_2 (4.5 ml), followed by the addition of trifluoro acetic acid (0.5 ml). The resulting mixture is refluxed under nitrogen for 1h, followed by the evaporation of solvents. The products is sufficiently pure for further use. An analytically pure sample can be obtained by filtration over a silica pad (CH_2Cl_2:EtOAc; 8:2 (v:v)). Orange solid; Mp 148°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.84 (s, 1H), 7.43 (m, 3H), 6.70 (d, 1H, J = 4 Hz), 6.67 (d, 1H, J = 4.28 Hz), 6.62 (d, 1H, J = 3.76 Hz), 6.47 (d, 1H, J = 2.52 Hz), 3.78 (d, 6H, J = 11.08 Hz), 3.72 (d, 2H, J = 23.16 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 154.0 (d), 143.6, 139.1, 135.2, 135.1, 134.0, 131.3, 131.2, 130.9, 128.6, 128.3, 121.4, 118.5, 60.4, 53.3 (d) ppm; LRMS (EI, 70 EV): 458 ; HRMS: Calculated for $C_{18}H_{16}BCl_2F_2N_2O_3P$ 458.0337, found 458.03253.

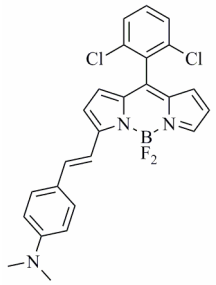
3-(2-phenyl vinyl)-8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 217a



Di-(*t*-Butyl)-malonate BODIPY (0.1 mmole) is dissolved in a mixture of DCM (4 ml) and TFA (1 ml), followed by stirring at room temperature overnight, or until full disappearance of starting material. The solvent is evaporated at room temperature, and the crude solid is suspended in toluene (1 ml), benzaldehyde (0.11 mmole, 1.1 equiv.) and piperidine (0.11 mmole, 1.1 equiv.) are added, followed by stirring at 50°C for 2 hours. The solvents

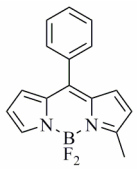
are evaporated, and the crude product is purified chromatographically (Silica; DCM/Petroleum ether; 1:1), a second column (Silica; Petroleum ether: Diethyl ether; 2:1). Purple solid; Mp 68°C; ^{1}H-NMR: δ 7.81 (s, 1H), 7.75 (d, 1H, J = 16.38 Hz), 7.64 (d, 2H, J = 7.92 Hz), 7.49-7.37 (m, 7H), 6.95 (d, 1H, J = 4.71 Hz), 6.70 (d, 1H, J = 4.71 Hz), 6.54 (d, 1H, J = 3.93 Hz), 6.54 (m, 1H) ppm; ^{13}C-NMR: δ 159.1, 141.3, 140.0, 137.0, 136.1, 135.9, 135.6, 133.7, 131.8, 131.1, 130.9, 130.0, 139.1, 128.3, 128.1, 126.5, 119.0, 118.4, 117.6 ppm; LRMS (EI, 70 EV): 438; HRMS: Calculated for $C_{23}H_{15}BCl_2F_2N_2$: 438.0673, found 438.06987.

3-(*p*-dimethylaminophenylethenyl)-8-(2,6-dichlorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 217b



Prepared in a similar manner as for the previous compound, isolated as a dark solid with bronze luster. Mp 201°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.70 (m, 1H), 7.56 (m, 2H), 7.44 (t, 2H, J = 9.72 Hz), 7.37 (m, 1H), 6.93 (d, 1H, J = 4.76 Hz), 6.69 (d, 2H, J = 8.84 Hz), 6.65 (d, 1H, J = 4.76 Hz), 6.40 (s, 1H), 3.06 (s, 6H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 161.0, 151.8, 142.0, 138.0, 137.4, 135.7, 132.8, 132.1, 130.8, 130.7., 130.2, 128.1, 123.8, 118.9, 116.1, 113.8, 111.9, 40.1 ppm; LRMS (EI, 70 EV): 481; HRMS: Calculated for $C_{25}H_{20}BCl_2F_2N_3$ 481.1095, found 481.10781.

3-methyl-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 218

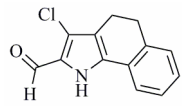


Obtained as a side product from the condensation reactions. Can also be prepared from the acid mediated decarboxylation of 3,5-di-*t*-butylmalonate-(BODIPY), stirring the compound in dichloromethane/TFA (9:1; 1 M solution) at reflux for 1h. Orange solid; Mp 77°C; ^{1}H-NMR: δ 7.79 (s, 1H), 7.52 (s, 4H), 6.88 (d, 1H, J = 4.32 Hz), 6.77 (d, 1H, J = 3.96 Hz), 6.48 (s, 1H), 6.36 (d, 1H, J = 4.32 Hz), 2.69 (s, 3H, CH_3) ppm; ^{13}C-NMR: δ 161.2, 144.4, 140.7, 133.9, 132.9, 130.4, 128.3, 121.0, 117.0, 15.3 ppm; LRMS (EI,

70 EV): 282; HRMS: Calculated for $C_{16}H_{13}BF_2N_2$ 282.1140, found 282.11501.

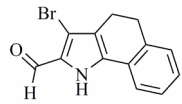
5.6. 1,7-disubstituted BODIPY dyes

3-Chloro-4,5-dihydro-1H-benzo[*g*]indole-2-carbaldehyde 181a



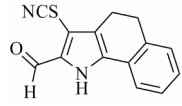
To a stirred solution of dihydrobenzindole aldehyde (197 mg, 1 mmole) and $NaHCO_3$ (102 mg, 1.2 mmol, 1.2 equiv.) in DCM (10 ml) is added sulfuryl chloride (1ml of a 1 M solution in DCM) while the temperature is kept at 0°C. The resulting mixture is stirred overnight, followed by pouring in aqueous $NaHCO_3$. Dichloromethane (50 ml) is added and the solution is extracted with water and brine. The organic layer is collected, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture is purified by column chromatography (Silica; DMC/EtOAc; 9:1, v/v). White crystalline solid (34%); Mp 207°C; ^{1}H-NMR: δ 10.60 (s, br, 1H, NH), 9.64 (s, 1H), 7.68 (d, 1H, J = 7.35 Hz), 7.30 (m, 3H), 2.98 (t, 2H, J = 7.35 Hz), 2.75 (t, 2H, J = 7.74 Hz) ppm; ^{13}C-NMR: δ 176.6, 137.4, 135.8, 128.9, 128.8, 127.7, 127.3, 126.7, 123.6, 121.8, 120.7 ppm; LRMS (EI, 70 EV): 231.

3-Bromo-4,5-dihydro-1H-benzo[*g*]indole-2-carbaldehyde 181b



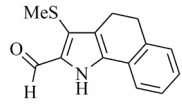
To a stirred solution of dihydrobenzindole aldehyde (394 mg, 2 mmole) and $NaHCO_3$ (168 mg, 2 mmol, 2 equiv.) in DCM (10 ml) is added bromine (320 mg, 2 mmol, 1 equiv.) while the temperature is kept at 0°C. The resulting mixture is stirred at room temperature for 2 hours, followed by pouring in aqueous $Na_2S_2O_3$. Dichloromethane (50 ml) is added and the solution is extracted with water and brine. The organic layer is collected, dried over $MgSO_4$, filtered and evaporated to dryness. The crude mixture is purified by column chromatography (Silica; DMC/EtOAc; 9:1, v/v). White crystalline solid (70%); Mp 210°C; ^{1}H-NMR: δ 10.14 (s, br, 1H, NH), 9.57 (s, 1H), 7.54 (d, 1H, J = 6.6 Hz), 7.26 (m, 3H), 2.99 (t, 2H, J = 7.53 Hz), 2.73 (t, 2H, J = 7.53 Hz) ppm; ^{13}C-NMR: δ 177.7, 137.4, 128.9, 128.9, 128.7, 127.3, 126.3, 115.9, 121.3, 110.0, 29.0, 19.9 ppm; LRMS (EI, 70 EV): 275.

3-Thiocyanato-4,5-dihydro-1H-benzo[*g*]indole-2-carbaldehyde 181d



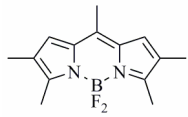
Iodine (189 mg, 0.745 mmole) is dissolved in MeOH (30 ml), followed by the addition of ammonium thiocyanate (170 mg, 2.235 mmole), and this solution is stirred at room temperature for 20 minutes followed by the addition of dihydrobenzindole aldehyde (294 mg, 1.49 mmole). The reaction mixture is stirred at room temperature overnight, followed by quenching with aqueous $Na_2S_2O_3$. After a standard extractive workup, the compound is purified chromatographically (silica, DCM/ EtOAc; 9:1, v/v) to yield the compound as grey needles (12.5%); Mp 188°C; ^{1}H-NMR: δ 11.13 (s, br, 1H, NH), 9.82 (s, 1H), 7.73 (d, 1H, J = 6.21 Hz), 7.29 (m, 3H), 3.03 (t, 2H, J = 7.17 Hz), 2.91 (t, 2H, J = 7.14 Hz) ppm; ^{13}C-NMR: δ 177.2, 137.2, 136.7, 132.1, 129.3, 128.9, 127.4, 126.6, 126.1, 122.0, 109.9, 109.8, 28.8, 19.6 ppm; LRMS (EI, 70 EV): 254.

3-Methylsulfanyl-4,5-dihydro-1H-benzo[*g*]indole-2-carbaldehyde 181c



Dihydrobenzindole thiocyanate (30 mg, 0.120 mmole), is dissolved in MeOH (1 ml), followed by the addition of MeI (18 mg, 8.2 µl , 1.1 equiv.) and KOH (8 mg, 1.3 equiv.). The solution is stirred overnight, and after a standard extractive workup, purified chromotographically (Silica; DCM/ EtOAc; 9:1 v/v). White needles (71%); Mp 146°C; ^{1}H-NMR: δ 10.4 (s, br, 1H, NH), 9.81 (s, 1H), 7.64 (d, 1H, J = 7.17 Hz), 7.28 (m, 3H), 2.99 (t, 2H, J = 7.71 Hz), 2.83 (t, 2H, J = 6.21 Hz), 2.37 (s, 3H) ppm; ^{13}C-NMR: δ 178.4, 137.4, 135.7, 132.3, 128.7, 128.5, 127.2, 127.1, 127.0, 126.0, 121.5, 29.4, 20.4, 19.9 ppm; LRMS (EI, 70 EV): 243.

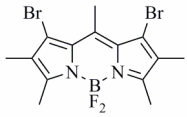
2,3,5,6,8-Pentamethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 178



2,3-Dimethylpyrrole (0.70 g, 7.5 mmole) is dissolved in DCM (10 ml), followed by the addition of acetyl chloride (0.291 g, 264 µl, 3.7 mmole). The mixture is refluxed for 2 hours, cooled to 0°C, followed by the addition of triethylamine (5 ml). After 10 minutes at 0°C, boron trifluoride etherate (5 ml) is added and the reaction mixture is stirred at room temperature

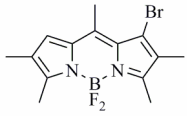
overnight. The solution is poured in diethylether (200 ml), and thoroughly washed with water. The organic layer is dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatographical purification yielded the compound as an orange solid (18%). Mp 165°C; ^{1}H-NMR: δ 6.82 (s, 2H), 2.49 (s, 6H), 2.35 (s, 3H), 2.02 (s, 6H) ppm; ^{13}C-NMR: δ 154.7, 137.5, 133.3, 127.1, 125.2, 15.0, 12.6, 11.2 ppm; LRMS (EI, 70 EV): 262; HRMS: Calculated for $C_{14}H_{17}BF_2N_2$ 262.14529, found 262.14499.

General procedure for the bromination of 1,7-unsubstituted BODIPY dyes: 1,7-dibromo-2,3,5,6,8-pentamethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 179a



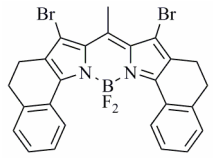
A solution of 2,3,5,6,8-pentamethyl BODIPY (0.178 g, 0.679 mmole) and $NaHCO_3$ (30 mg, 1.5 mmole, 2.2 equiv.) is stirred at 0°C, followed by the slow addition of bromine (217 mg, 1.36 mmole, 2 equiv.). The resulting reaction mixture is stirred at room temperature for 2 hours, followed by quenching of the reaction with an aqueous $Na_2S_2O_3$ solution. The organic layer is extracted with water, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product is purfied by column chromatography (silica, CH_2Cl_2-petroleum ether, (1:1)). Red solid (82%); Mp >300°C; ^{1}H-NMR: δ 3.08 (s, 3H), 2.52 (s, 6H), 2.05 (s, 6H) ppm; ^{13}C-NMR: δ 152.8, 141.7, 129.1, 118.9, 16.6, 13.2, 10.9 ppm; LRMS (EI, 70 EV): 420; HRMS: Calculated for $C_{14}H_{15}BBr_2F_2N_2$: 417.96631, found 419.96913.

1-Bromo-2,3,5,6,8-pentamethyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 179b



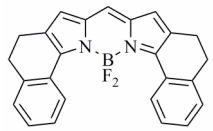
Obtained from the general procedure for the bromination of 1,7-unsubstituted BODIPY dyes (only one equiv. of bromine) as a red solid. Mp 195°C; ^{1}H-NMR: δ 6.99 (s, 1H), 2.68 (s, 3H), 2.53 (s, 3H), 2.49 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H) ppm; ^{13}C-NMR: δ 157.0, 151.1, 129.2, 134.3, 128.5, 127.2, 127.0, 117.3, 17.0, 13.0, 12.8, 11.3, 10.6 ppm; LRMS (EI, 70 EV): 340, 342; HRMS: Calculated for $C_{14}H_{16}BBrF_2N_2$: 340.05580, found 340.0558.

Bis-(dihydronaphthyl)-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-_s_-indacene 179d



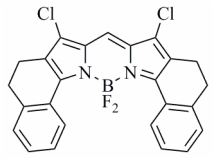
Obtained from the general procedure for the bromination of 1,7-unsubstituted BODIPY dyes as a dark metallic solid (quantitative yield); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.69 (d, 2H, J = 7.8 Hz), 7.39 (t; 2H, J = 7.32 Hz), 7.30 (t, 2H, J = 7.32 Hz), 7.24 (d, 2H, J = 6.8 Hz), 3.21 (s, 3H), 2.90 (t, 4H, J = 6.8 Hz), 2.70 (t, 4H, J = 5.8 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 149.9, 140.9, 140.7, 134.4, 131.9, 130.2, 128.8, 128.7, 128.6, 128.4, 127.6, 127.5, 115.5, 30.1, 22.0, 18.0 ppm.

General procedure for condensation on pyrrolic aldehydes to symmetric BODIPY dyes: _Bis_-(dihydronaphthyl)-8-methyl-4,4-difluoro-4-bora-3a,4a-diaza-_s_-indacene



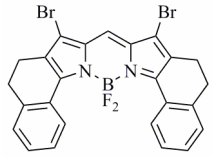
Dihydroxybenzindole aldehyde (164 mg, 0.83 mmole) is dissolved in DCM (5 ml). Phosphorus oxychloride (307 mg, 2.4 equiv.) is added and the reaction mixture is stirred overnight. To the blue solution, triethylamine is added (708 mg, 0.973 ml, 10 equiv.), 10 minutes later followed by boron trifluoride etherate (0.975 ml, 11 equiv. at 0°C. The mixture is stirred at room temperature overnight, after which it is extracted with DCM (100 ml) and water (4 x 200 ml). The organic layer is collected, dried over $MgSO_4$, filtered and evaporated to dryness. The crude solid is purified chromatographically (Silica; petroleum ether/ ethyl ecetate (8:2; v/v)). Green solid with copper luster; Mp 278°C; ^{1}H-NMR: δ 8.75 (d, 2H, J = 7.89 Hz), 7.43 (t, 2H, J = 6.39 Hz), 7.29 (m, 4H), 6.99 (s, 1H), 6.78 (s, 2H), 2.92 (t, 4H, J = 6.21 Hz), 2.73 (t, 4H, J = 7.53 Hz) ppm; ^{13}C-NMR: δ 143.4, 141.6, 136.4, 133.1, 129.8, 128.3, 127.5, 124.9, 124.1, 30.5, 22.4 ppm; LRMS (EI, 70 EV): 396.

Bis-(dihydronaphthyl)-1,7-dichloro-4,4-difluoro-4-bora-3a,4a-diaza-_s_-indacene 182a



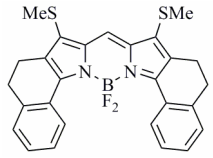
Obtained by following the general procedure for the condensation of pyrrolic aldehydes to symmetric BODIPY dyes, as a deep blue metallic solid. Mp 305°C; ^{1}H-NMR: δ 8.70 (d, 2H, J = 7.92 Hz), 7.46-7.24 (m, 7H), 2.94 (, 4H, J = 6.39 Hz), 2.73 (, 4H, J = 3.69 Hz) ppm; ^{13}C-NMR: δ 151.8, 140.8, 133.3, 130.6, 129.8, 128.6, 128.5, 128.3, 127.7, 127.6, 117.6, 34.2, 20.2 ppm; LRMS (EI, 70 EV): 396.

Bis-(dihydronaphthyl)-1,7-dibromo-4,4-difluoro-4-bora-3a,4a-diaza-_s_-indacene 182b



Obtained by following the general procedure for the condensation of pyrrolic aldehydes to symmetric BODIPY dyes, as a bronze metallic solid. Mp 283°C; ^{1}H-NMR: δ 8.70 (d, 2H, J = 7.71 Hz), 7.45-7.24 (m, 7H), 2.95 (t, 4H, J = 6.39 Hz), 2.72 (t, 4H, J = 5.67 Hz) ppm; ^{13}C-NMR: δ 152.4, 141.5, 13.5.1, 133.2, 121.0, 129.0, 128.7, 128.5, 128.4, 127.7, 127.7, 120.3, 117, 30.15, 21.7 ppm; LRMS (EI, 70 EV): 556.

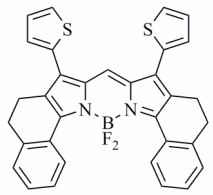
Bis-(dihydronaphthyl)-1,7-bis-(methylsulfanyl)-4,4-difluoro-4-bora-3a,4a-diaza-_s_-indacene 182c



Obtained by following the general procedure for the condensation of pyrrolic aldehydes to symmetric BODIPY dyes, as a bronze metallic solid. Mp >300°C; ^{1}H-NMR: δ 7.71 (d, 2H, J = 6.24 Hz), 7.68 (d, 1H, J = 3.03 Hz), 7.28 (m, 4H), 2.93 (t, 4H, J = 4.32 Hz), 2.84 (t, 4H, J 4.14 Hz), 2.40 (s, 6H)

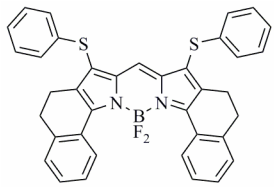
ppm; ^{13}C-NMR: δ 152.0, 140.7, 137.7, 135.9, 133.2, 130.2, 128.4, 128.0, 127.7, 119.4, 30.3, 21.4, 20.1 ppm; LRMS (EI, 70 EV): 488.

Bis-(dihydronaphthyl)-1,7-bis-(2-thienyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 183



Obtained from the standard procedure for Stille coupling, as a blue metallic solid (64%). Mp 305°C; ^{1}H-NMR: δ 8.30 (d, 2H), 7.77 (s, 1H), 7.48 (m, 4H), 7.34-7.16 (m, 8H), 2.95-.289 (m, 8H) ppm; ^{13}C-NMR: δ 140.6, 133.9, 130.1, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 127.3, 31.0, 21.5 ppm; LRMS (EI, 70 EV): 560; HRMS: Calculated for $C_{33}H_{23}BF_2N_2S_2$ 560.13638, found 560.13948.

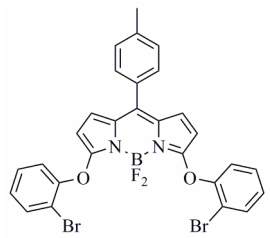
***Bis*-(dihydronaphthyl)-1,7-bis-(phenylsulfanyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 184**



Obtained from the standard nucleophilic substitution procedure with triethylamine as base and 4 equivalents of thiophenol. Golden metallic solid (16%); ^{1}H-NMR: δ 8.76 (d, 2H, J = 7.92 Hz), 7.58 (s, 1H), 7.43 (t, 2H, J = 7.53 Hz), 7.36-7.13 (m, 14H), 2.87 (t, 4H, J = 6.57 Hz), 2.58 (t, 4H, J =7.53 Hz) ppm; ^{13}C-NMR: δ 152.5, 140.9, 138.4, 136.7, 136.1, 130.4, 129.3, 128.9, 128.5, 128.0, 127.9, 127.7, 126.3, 123.1, 120.0, 30.0, 21.3 ppm.

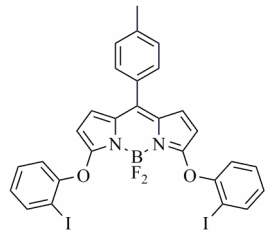
5.7. Restricted BODIPY dyes

3,5-*bis*-(*o*-Bromophenylether)-8-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 188a



To a stirred solution of 3,5-dichloro-4,4-difluoro-8-(4-tolyl)- bora-3*a*,4*a*-diaza-*s*-indacene (700 mg, 2 mmol) in acetonitrile (20 ml) is added 2-bromophenol (4 mmol, 354 mg, 2 equivs.), followed by Na_2CO_3 (2.2 equivs., 466 mg). The resulting mixture is stirred at reflux for 1 hour or until TLC-analysis indicates complete reaction. The solvent is evaporated *in vacuo* and the residual solid is purified by chromatography (silica, CH_2Cl_2-petroleum ether, 1:1) to yield an orange solid (585 mg, 94%). Mp 192 °C; ^{1}H NMR: δ 7.66 (d, 2H, *J* = 8.22 Hz), 7.40-7.34 (m, 6H), 7.28 (d, 2H, *J* = 9.12 Hz), 7.19-7.12 (m, 2H), 6.71 (d, 2H, *J* = 3.66 Hz), 5.54 (d, 2H, *J* = 4.56 Hz), 2.43 (s, 3H) ppm; ^{13}C NMR: δ 163.1, 151.8, 141.7, 140.3, 134.2, 130.5, 130.4, 129.1, 128.9, 128.4, 127.4, 122.7, 115.6, 102.6, 21.5 ppm; LRMS (EI, 70 EV): 624; HRMS: Calculated for $C_{28}H_{19}O_2N_2BF_2Br_2$ 621.9874, found 621.9896.

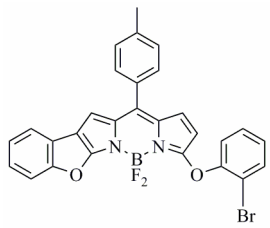
3,5-*bis*-(*o*-Iodophenylether)-8-*(p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 188b



To a stirred solution of 3,5-dichloro-4,4-difluoro-8-(4-tolyl)-bora-3*a*,4*a*-diaza-*s*-indacene (175 mg, 0.5 mmol) in acetonitrile (20 ml) is added 2-iodophenol (1.1 mmol, 242 mg, 2.2 equivs.), followed by Na_2CO_3 (2.2 equivs., 233 mg). The resulting mixture is stirred at reflux for 1 hour or until TLC-analysis indicates complete reaction. The solvent is evaporated *in vacuo* and the residual solid is purified by chromatography (silica,

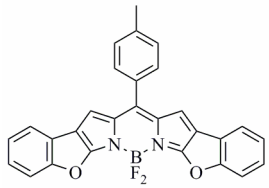
CH_2Cl_2/Petroleum ether, 1:1) to yield an orange solid (330 mg, 92 %). Mp 191 °C; ^{1}H NMR: δ 7.89 (d, 2H, *J* = 7.3 Hz), 7.38 (m, 4H), 7.31-7.26 (m, 4H), 7.00 (t, 2H, *J* = 7.3 Hz), 6.71 (d, 2H, *J* = 4.6 Hz), 5.53 (d, 2H, *J* = 4.6 Hz), 2.43 (s, 3H, tolyl-CH_3) ppm; ^{13}C NMR: δ 163.1, 154.7, 140.3, 130.5, 130.3, 129.9, 129.1, 129.5, 127.7, 121.8, 102.8, 89.1, 21.5 ppm; MS (ESI): 718 (M), 741 (M+Na).

3-(*o*-bromophenylether)-[5,6]-benzofuranyl-8-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 189



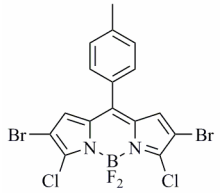
To a stirred solution of **186** (62 mg, 0.1 mmol) in dioxane (2 ml) is added $Pd(OAc)_2$ (1.2 mg, 5 mol%), triphenylphosphine (2.1 mg, 10 mol%) and K_2CO_3 (41 mg, 0.3 mmol, 3 equivs.). The resulting suspension is stirred at reflux for 96 hours. The reaction mixture is poured in diethyl ether (100 ml) and washed with water (2 × 100 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual solid is purified by chromatography (silica, CH_2Cl_2/Petroleum ether, 1:1) to yield shiny dark crystals (17 mg, 32%). Mp: 277 °C; ^{1}H NMR (400 MHz): δ 7.67 (d, 1H, *J* = 7.32 Hz), 7.54 (t, 2H, *J* = 9.15 Hz), 7.48-7.40 (m, 2H),7.40-7.34 (m, 2H),7.32 (d, 2H, *J* = 8.22 Hz) 7.28-7.25 (m, 2H), 7.22-7.15 (m, 1H), 6.83 (s, 1H), 6.76 (d, 1H, *J* = 3.66 Hz), 5.58 (d, 1H, *J* = 4.56 Hz), 2.47 (s, 3H, tolyl-CH_3) ppm; ^{13}C NMR (100 MHz): δ 166.7, 136.9, 160.8, 151.5, 143.8, 140.5, 134.3, 133.7, 131.6, 130.6, 130.4, 129.0, 127.7, 126.1, 124.4, 122.9, 121.8, 121.3, 117.7, 117.3, 115.8, 113.1, 103.3, 21.5 ppm; LRMS (EI, 70 EV): 542; HRMS: Calculated for $C_{28}H_{18}BBrF_2N_2O_2$ 542.0613, found 542.0627.

Bis-(benzofurano[2,3-b])-8-(_p_-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-_s_-indacene 190



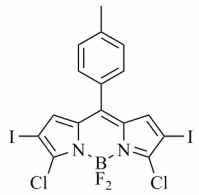
To a stirred solution of **186** (62 mg, 0.1 mmole) in toluene (2 ml) is added $Pd(OAc)_2$ (1.2 mg, 5 mol%), triphenylphosphine (2.1 mg, 10 mol%) and K_2CO_3 (41 mg, 0.3 mmol, 3 equivs.). The resulting suspension is stirred at reflux for 48 hours. The purple reaction mixture is poured in diethyl ether (100 ml) and washed with water (2 × 100 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual solid is purified by chromatography (silica, CH_2Cl_2-petroleum ether, 1:1 v/v) to yield dark crystals with a golden luster (32 mg, 69%). Mp 263-265 °C; ^{1}H NMR: δ 7.58-752 (m, 6H), 7.39-7.24 (m, 6H), 6.87 (s, 2H), 2.51 (s, 3H, tolyl-CH_3) ppm; ^{13}C NMR: 167.6, 161.2, 140.8, 134.7, 130.9, 130.7, 129.3, 126.5, 124.6, 121.7, 121.6, 118.5, 118.3, 113.1, 21.5 ppm; LRMS (EI, 70 EV): 462; HRMS: Calculated for $C_{28}H_{17}O_2N_2BF_2$ 462.1351, found 462.1370.

2,6-Dibromo-3,5-dichloro-8-(_p_-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-_s_-indacene 195a



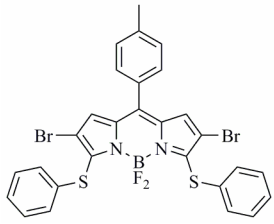
Dichloro-BODIPY (0.5 mmol, 175 mg) was dissolved in THF (10 ml). NBS (2 equivs, 178 mg, 1 mmole) was added and the mixture was refluxed for 48 hours. After completion of the reaction, the solvent was evaporated in vacuo and the solid was purified by column chromatography (Silica, CH_2Cl_2:Petroleum Ether, 1:1 v/v) to yield the desired product as red crystals with a green luster. Mp 231°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.36 (m, 4H), 6.95 (s, 2H), 2.47 (s, 3H, Tolyl-CH_3) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 144.5, 144.1, 142.6, 132.8, 131.7, 130.6, 129.7, 128.9, 108.0, 21.6 ppm; LRMS (EI, 70 EV): 508; HRMS: Calculated for $C_{16}H_9BBr_2Cl_2F_2N_2$ 505.8571, found 505.85707.

2,6-Diiodo-3,5-dichloro-8-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 195b



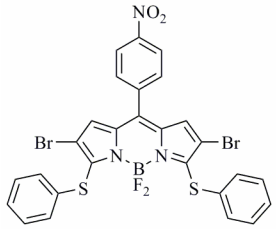
To a solution of 3,5-dichloro-8-tolyl BODIPY (350 mg, 1 mmole) in DCM (10 ml) is added $NaHCO_3$ (200 mg, 2.30 mmole, 2.3 equiv.), and the mixture is stirred at 0°C, followed by the slow addition of iodine monochloride (217 mg, 1.36 mmole, 2 equiv., as a solution in DCM). The resulting reaction mixture is stirred at room temperature for 2 hours, followed by quenching of the reaction with an aqueous $Na_2S_2O_3$ solution. The organic layer is extracted with water, dried over $MgSO_4$, filtered and evaporated to dryness. The compound is sufficiently pure for further use. Red solid with green luster; Mp 299-301°C; ^{1}H-NMR: δ 7.36 (m, 4H), 7.06 (s, 2H), 2.47 (s, 3H) ppm; ^{13}C-NMR: δ 163.6, 148.5, 143.3, 142.7, 138.3, 135.1, 130.9, 130.1, 129.3, 21.9 ppm; LRMS (EI, 70 EV): 602; HRMS: Calculated for $C_{16}H_9BCl_2F_2I_2N_2$ 601.8293, found 601.83259.

2,6-Dibromo-3,5-bis-*S*-phenylthioether-8-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



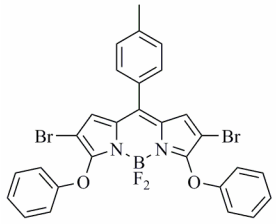
Obtained from 3,5-dichloro-2,6-dibromo-8-tolyl BODIPY, by using the general procedure for nucleophilic aromatic substitution developed for *bis*-ether **186**. Deep purple solid; ^{1}H-NMR: δ 7.45 (m, 4H), 7.39 (d, 2H, J = 8.22 Hz), 7.32 (d, 2H, J = 8.22 Hz), 7.28 (m, 6H), 6.94 (s, 2H), 2.44 (s, 3H, Tolyl-CH_3) ppm; ^{13}C-NMR: δ 150.5, 142.3, 142.0, 135.1, 132.7, 132, 0, 131.5, 130.6, 129.8, 129.6, 129.3, 127.9, 114.5, 21.6 ppm; LRMS (EI, 70 EV): 656; HRMS: Calculated for $C_{28}H_{19}BBr_2F_2N_2S_2$ 653.9418, found 655.94442.

2,6-Dibromo-3,5-bis-*S*-phenylthioether-(*p*-nitrophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



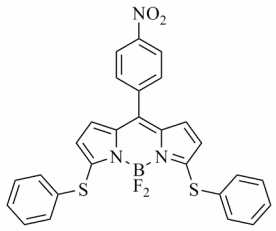
Obtained from 3,5-dichloro-2,6-dibromo-8-nitrophenyl BODIPY, by using the general procedure for nucleophilic aromatic substitution developed for *bis*-ether **186**. Dark Solid; Mp 203°C; ^{1}H-NMR: δ 8.389 (d, 2H, J = 8.22 Hz), 7.70 (d, 2H, J = 9.12 Hz), 7.348 (m, 4H), 7.33 (m, 6H), 6.82 (s, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 152.7, 149.2, 138.7, 137.2, 134.5, 131.9, 131.8, 131.2, 131.2, 129.3, 128.3, 123.9, 114.9 ppm; LRMS (EI, 70 EV): 685.

2,6-Dibromo-3,5-bis-phenylether-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



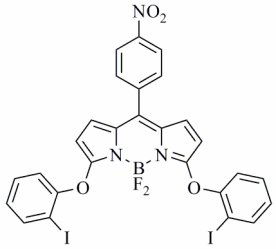
Obtained from 3,5-dichloro-2,6-dibromo-8-tolyl BODIPY, by using the general procedure for nucleophilic aromatic substitution developped for *bis*-ether **186**. Deep red crystals (Quant.); ^{1}H-NMR: δ 7.42 (d, 2H, , J = 8.22 Hz), 7.35-7.29 (m, 6H), 7.15-7.08 (m, 6H), 6.93 (s, 2H), 2.46 (s, 3H, Tolyl-CH_3) ppm; ^{13}C-NMR: δ 157.8, 155.7, 142.6, 141.5, 132.0, 130.5, 129.7, 129.5, 129.4, 127.6, 124.5, 117.8, 96.0, 21.6 ppm; LRMS (EI, 70 EV): 624; HRMS: Calculated for $C_{28}H_{19}BBr_2F_2N_2O_2$ 621.9874, found 623.98516.

3,5-Bis-phenylthioether-8-(*p*-nitrophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



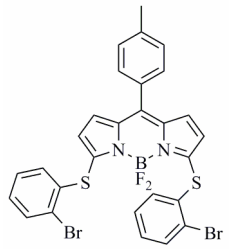
Obtained from 3,5-dichloro-8-nitrophenyl BODIPY, by using the general procedure for nucleophilic aromatic substitution developed for *bis*-ether **186**. Dark solid; ^{1}H-NMR: δ 8.31 (d, 2H, J = 8.22 Hz), 7.65 (m, 6H), 7.44 (m, 6H), 6.50 (d, 2H, J = 4.56 Hz), 8.87 (d, 2H, J = 4.59 Hz) ppm; ^{13}C-NMR: δ 158.7, 148.7, 140.3, 135.6, 135.1, 134.7, 131.0, 129.9, 129.8, 128.5, 123.7, 119.1 ppm.

3,5-Bis-(*o*-iodophenylether)-8-(*p*-nitrophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene



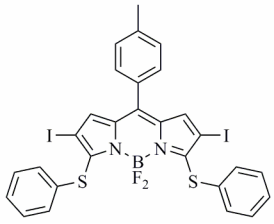
Obtained from 3,5-dichloro-8-nitrophenyl BODIPY, by using the general procedure for nucleophilic aromatic substitution developed for *bis*-ether **186**. Red solid; Mp 126°C; ^{1}H-NMR: δ 8.35 (d, 2H, J = 8.22 Hz), 7.90 (d, 2H, J = 7.29 Hz), 7.70 (d, 2H, J = 8.22 Hz), 7.21 (m, 2H), 7.03 (t, 2H), 6.61 (d, 2H, J = 4.59 Hz), 5.57 (d, 2H, J = 4.56 Hz) ppm; ^{13}C-NMR: δ 164.0, 154.4, 148.8, 140.3, 139.7, 137.6, 131.4, 130.1, 129.9, 128.1, 123.7, 121.9, 103.8, 89.1 ppm.

3,5-Bis-(*o*-bromophenylthioether)-8-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 191a



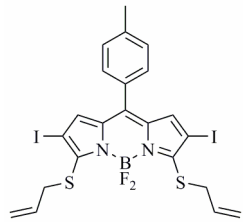
Golden crystals; ^{1}H-NMR: δ 7.70-7.64 (m, 4H), 7.38-7.22 (m, 8H), 6.70 (d, 2H, J : 3.63 Hz), 5.94 (d, 2H, J = 4.56 Hz), 2.43 (s, 3H) ppm; ^{13}C-NMR: δ 154.1, 140.6, 139.8, 136.5, 135.9, 133.9, 133.0, 130.8, 130.7, 130.4, 129.6, 129.2, 128.5, 128.4, 119.0, 21.5 ppm; LRMS (EI, 70 EV): 656; HRMS: Calculated for $C_{28}H_{19}BBr_2F_2N_2S_2$: 656.9648, found 656.96523

2,6-Diiodo-3,5-bis-(*o*-bromophenylether)-8-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 194a



Obtained from the standard procedure for nucleophilic substitution with triethylamine as base and thiophenol as nucleophile. Blue solid with green luster; Mp 226-228°C; ^{1}H-NMR: δ 7.40 (m, 6H), 7.31 (m, 8H), 7.12 (s, 2H), 2.45 (s, 3H) ppm; ^{13}C-NMR: δ 153.3, 142.0, 141.8, 138.7, 137.2, 133.5, 131.2, 130.6, 129.9, 129.6, 129.3, 127.7, 84.2, 21.6 ppm.

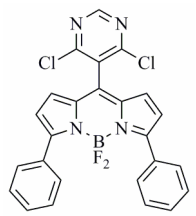
2,6-Diiodo-3,5-bis-(allylthioether)-8-(*p*-tolyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 194b



Obtained from the standard procedure for nucleophilic substitution with triethylamine as base and allylthiol as nucleophile. Blue crystals with bronze luster; Mp 168-169°C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.37 (d, 2H, J = 8.04 Hz), 7.32 (d, 2H, J = 8.04 Hz), 7.06 (s, 2H), 6.00 (m, 2H), 5.25 (dd, 2H, J = 16.84 Hz, J = 1.24 Hz), 5.06 (d, 2H, J = 10.08 Hz), 3.86 (d, 2H, J = 7.28 Hz), 2.46 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 154.9, 141.8, 141.1, 137.7, 137.4, 133.2, 130.7, 130.0, 129.5, 118.8, 85.6, 39.9, 21.6 ppm.

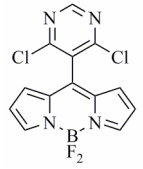
5.8. Pyrimidinyl BODIPY

BODIPY synthesis: General procedure: 3,5-diphenyl-8-(4,6-dichloropyrimidin-5-yl)-BODIPY 227c



4,6-Dichloropyrimidine-5-aldehyde (1.77 g, 10 mmol) and 2-phenylpyrrole (2.86 g, 20 mmol, 2 equivs.) are dissolved in 100 ml of CH_2Cl_2 under a nitrogen atmosphere. A few drops of trifluoroacetic acid are added, and the reaction is followed by TLC. After the disappearance of the starting material, DDQ (2.27 g, 10 mmol) is added and the mixture is stirred at room temperature for 2 h. The reaction mixture is cooled to 0 °C using an ice bath, and triethylamine (14 ml, 100 mmol, 10 equivs.) is added and the solution is left stirred for 10 min, after witch boron trifluoride etherate (14 ml, 110 mmol, 11 equivs.) is added dropwise. The icebath is removed and the reaction is stirred during 5 days at room temperature. The solution is taken up in 300 ml diethyl ether, and washed with water (3 × 200 ml), dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue is purified by column chromatography (silica, dichloromethane/petroleum ether, 1:1 v/v) to yield 2.060 g of the BODIPY (80 % total yield) as a purple crystalline solid. Mp 102 °C. ^{1}H-NMR: δ 8.98 (s, 1H, H-1'), 7.91(m, 4H), 7.44 (m, 6H), 6.67 (s, 4H) ppm; ^{13}C-NMR: δ 162.2, 161.1, 158.8, 135.2, 132.1, 131.7, 130.3, 139.7, 128.5, 127.5, 122.4 ppm; LRMS (EI, 70 EV): 490; HRMS: Calculated for $C_{25}H_{15}N_4BF_2Cl_2$ 490.07349, found 490.07346.

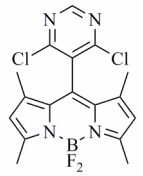
8-(4,6-Dichloropyrimidin-5-yl)-BODIPY 227a



To 250 ml of distilled water is added 1 ml of HCl (37%) and the solution is stirred under nitrogen for 10 min. Pyrrole (2.1 ml, 30 mmol) is added to the water and stirred until a clear solution is obtained. Then, 4,6-

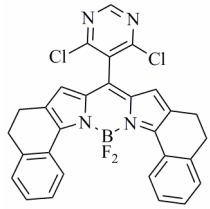
dichloropyrimidine-5-carbaldehyde (1.77 g, 10 mmol) is added in portions over 10 min. After a few min, the clear solution becomes opaque, and a precipitate begins to form. The mixture is stirred at room temperature for 6 h, filtered over a glass filter and thoroughly washed with water. The solid can be dried under vacuum to yield sufficiently pure dipyrromethane. Further purification can be effected by dissolving the crude solid in dichloromethane, drying over $MgSO_4$, filtering and evaporating to dryness. This solid is then stirred in petroleum ether for 6 h to remove trace impurities. From hereon the general procedure is followed, starting with the oxidation by DDQ. After oxidation and complexation, the product is obtained (745 mg, 22% from the starting aldehyde) as a red solid. Mp 108 °C. ^{1}H-NMR: δ 8.98 (s, 1H, H-1'), 8.01 (m, 2H), 6.72 (m, 2H), 6.58 (m, 2H) ppm; ^{13}C-NMR: δ 159.3, 147.2, 139.9, 120.4 ppm; LRMS (EI, 70 EV): 338, HRMS: Calculated for $C_{13}H_7BCl_2F_2N_4$ 338.01089, found 338.01076.

1,3,5,7-Tetramethyl-8-(4,6-dichloropyrimidin-5-yl)-BODIPY 227b



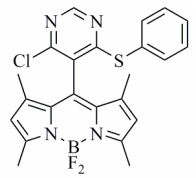
According to the general procedure, 1.18 g of BODIPY (30% total yield) was obtained as a red solid. Mp 142 °C. ^{1}H-NMR: δ 8.93 (s, 1H, H-1'), 6.07 (s, 2H), 2.59 (s, 6H), 1.54 (s, 6H) ppm; ^{13}C-NMR: δ 161.6, 158.5, 158.1, 141.1, 129.8, 128.7, 122.3, 15.0, 14.1 ppm; LRMS (EI, 70 eV): 394; HRMS: Calculated for $C_{17}H_{15}N_4BF_2Cl_2$ 394.0735 found 394.07362.

***Bis*-[dihydronaptho]-8-(4,6-dichloropyrimidin-5-yl)-BODIPY 227d**



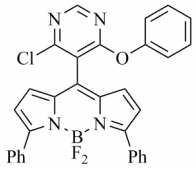
According to the general procedure, 1.303 g of BODIPY (48% total yield for a 5 mmol reaction) was obtained as a blue solid. Mp >300 °C ^{1}H-NMR: δ 8.95 (s, 1H, H-1'), 8.80 (d, J = 7.8 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.29 (s, 2H), 6.31 (s, 2H), 2.94 (t, J = 6.6 Hz,4H), 2.70 (t, J = 6.6 Hz, 4H) ppm; LRMS (EI, 70 EV): 542; HRMS: Calculated for $C_{29}H_{19}N_4BF_2Cl_2$ 542.1048, found 542.10487.

1,3,5,7-Tetramethyl-8-(4-phenylsulfanyl-6-chloropyrimidin-5-yl)-BODIPY



1,3,5,7-Tetramethyl-8-dichloropyrimidinyl BODIPY (79 mg, 0.2 mmol) is dissolved in 5 ml of DMF, followed by the addition of thiophenol (103 µl, 0.5 mmol, 2.5 equivs.) and K_2CO_3 (69 mg, 0.5 mmol). The mixture is stirred at 100 °C under a nitrogen atmosphere for 4 h. After disappearance of the starting material, the mixture is poured in diethyl ether, and washed with water (3 × 100 ml), dried, filtered and evaporated until dryness. The crude product is purified by column chromatography (silica, dichloromethane/petroleum ether, 1:1 v/v) to yield the BODIPY (15 mg, 16%) as a red solid. Mp 235 °C. ^{1}H-NMR: δ 8.68 (s, 1H, H-1'), 7.46 (m, 5H), 6.09 (s, 2H), 2.61 (s; 6H), 1.68 (s, 6H) ppm; ^{13}C-NMR: δ 172, 158.5, 157.9, 141.4, 135.8, 130.4, 130.3, 129.9,129.7, 126.6, 124.7, 122.1, 15.1, 14.2 ppm; LRMS (EI, 70 EV): 468; HRMS: Calculated for $C_{23}H_{20}N_4BF_2ClS$ 468.1158, found 468.11591.

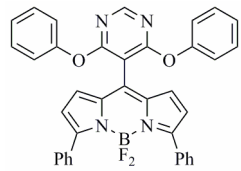
General procedure for nucleophilic substitution on the *meso*-(2,6-dichloropyrimidine): 3,5-diphenyl-8-(4-phenoxy-6-chloropyrimidin-5-yl)-BODIPY 228a



3,5-Diphenyl-8-dichloropyrimidinyl BODIPY (98 mg, 0.2 mmol) is dissolved in 5 ml of DMF, followed by the addition of phenol (18.8 mg, 0.2 mmol, 1 equivs.), K_2CO_3 (28 mg, 0.2 mmol) and a catalytic amount of 18-crown-6 (2.64 mg, 0.01 mmol, 5%). The mixture is stirred at room temperature until the starting material has disappeared. The mixture is poured in diethyl ether and washed with water (3 × 100 ml), dried, filtered and evaporated until dryness. The crude product is purified by flash column (silica, dichloromethane/petroleum ether, 1:1 v/v) to yield the BODIPY (107.4 mg, 98%) as a purple solid. Mp 130 °C. ^{1}H-NMR: δ 8.70 (s, 1H, H-1') 7.91 (d, J = 4.5 Hz, 4H), 7.43 (m, 8H), 7,29 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 2H), 7.85 (d, J = 3.6 Hz, 2H), 6.68 (d, J = 3.6 Hz, 2H) ppm; ^{13}C-

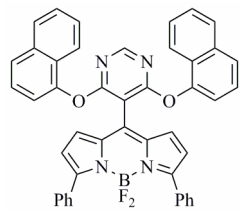
NMR: δ 168.5, 161.6, 160.5, 158.7, 152.0, 135.9, 132.3, 131.8, 130.1, 129.9, 129.6, 128.6, 128.5, 126.6, 122.0, 121.6, 114.8 ppm; LRMS (EI, 70 EV): 548; HRMS: Calculated for $C_{31}H_{20}N_4BF_2ClO$ 548.1387, found 548.13968.

3,5-Diphenyl-8-(4,6-bis-phenoxy-pyrimidin-5-yl)-BODIPY 228a



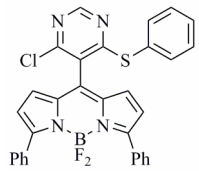
Obtained from 3,5-diphenyl-8-dichloropyrimidinyl BODIPY, by using the general procedure for nucleophilic aromatic substitution. Purple solid (103 mg, 85%). Mp 218 °C. ^{1}H-NMR: δ 8.51 (s, 1H, H-1'), 7.90 (d, *J* = 5.7 Hz, 4H), 7.41 (m, 10 H), 7.24 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 4H), 7.04 (d, *J* = 3.3 Hz, 2H), 6.69 (d, *J* = 3 Hz, 2H) ppm; ^{13}C-NMR: δ 168.9, 159.8, 158.6, 152.5, 136.7, 132.5, 132.2, 129.8, 129.6, 128.9, 128.4, 126.2, 121.7, 121.6, 100.7 ppm; LRMS (EI, 70 EV): 606; HRMS: Calculated for $C_{37}H_{25}N_4BF_2O_2$ 606.2089, found 606.20569.

3,5-Diphenyl-8-(4,6-bis-2-naphthoxy-pyrimidin-5-yl)-BODIPY 228b



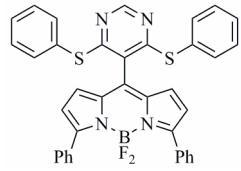
Obtained from model dye 3,5-diphenyl-8-dichloropyrimidinyl BODIPY, by using the general procedure for nucleophilic aromatic substitution. Purple solid (106 mg, 75%). Mp 134 °C. ^{1}H-NMR (600 MHz): δ 8.55 (s, 1H, H-1'), 7.98 (d, *J* = 6.6 Hz, 4H), 7.93 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.63 (s, 2H), 7.49-7.55 (m, 4H), 7.43-7.49 (m, 6H), 7.32 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 4.2 Hz, 2 H), 6.79 (d, *J* = 4.2 Hz, 2H) ppm; ^{13}C-NMR: δ 169.0, 159.9, 158.5, 150.0, 136.7, 133.9, 132.5, 132.1, 131.6, 129.9, 129.8, 129.6, 128.9, 128.4, 128.0, 127.7, 126.9, 126.0, 121.6, 121.1, 117.5, 100.8 ppm; MS (ESI) 707.

3,5-Diphenyl-8-(4-phenylsulfanyl-6-chloropyrimidin-5-yl)-BODIPY 228b



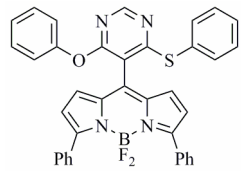
Obtained from model dye 3,5-diphenyl-8-dichloropyrimidinyl BODIPY, by using the general procedure for nucleophilic aromatic substitution. Purple solid (101 mg, 90%). Mp 230 °C. ^{1}H-NMR: δ 8.73 (s, 1H, H-1'), 7.93 (d, *J* = 3.9Hz, 4H), 7.43-7.50 (m, 11H), 6.80 (s, 2H), 6.69 (s, 2H) ppm; ^{13}C-NMR: δ 173.1, 160.8, 159.3, 158.1, 135.7, 135.3, 132.7, 132.2, 130.3, 130.2, 129.7, 129.6, 128.7, 128.5, 127.1, 123.8, 122.2 ppm; LRMS (EI, 70 EV) 564; HRMS: Calculated for $C_{31}H_{20}N_4BF_2ClS$ 564.1158, found 564.11681.

3,5-Diphenyl-8-(4,6-bis-phenylsulfanyl-pyrimidin-5-yl)-BODIPY 229c



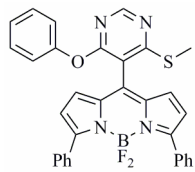
Obtained from 3,5-diphenyl-8-dichloropyrimidinyl BODIPY, by using the general procedure for nucleophilic aromatic substitution. Purple solid (115 mg, 90%). Mp 192 °C. ^{1}H-NMR (600 MHz): δ 8.59 (s, 1H, H-1'), 7.95 (d, *J* = 7.2 Hz, 4H), 7.49 (d, *J* = 6.6 Hz, 4H), 7.45 (m, 6H), 7.40 (m, 2H), 6.93 (d, *J* = 3.6 Hz, 2H), 6.71 (d, *J* = 3.6 Hz, 2H) ppm; ^{13}C-NMR (150 MHz): δ 168.9, 160.5, 157.7, 135.6, 135.5, 132.4, 130.0, 129.8, 129.7, 129.4, 128.9, 128.4, 128.0, 122.0, 121.8 ppm; LRMS (EI, 70 EV): 638; HRMS: Calculated for $C_{37}H_{25}N_4BF_2S_2$ 638.1582, found 638.15739.

3,5-Diphenyl-8-(4-phenoxy-6-phenylsulfanyl-pyrimidin-5-yl)-BODIPY 229d



3,5-Diphenyl-8-dichloropyrimidinyl BODIPY (98 mg, 0.2 mmol) is dissolved in 5 ml of DMF, followed by the addition of phenol (18.8 mg, 0.2 mmol, 1 equivs.), K_2CO_3 (56 mg, 0.4 mmol) and a catalytic amount of 18-crown-6 (2.64 mg, 0.01 mmol, 5%). The mixture is stirred at 100 °C until TLC analysis indicates complete disappearance of the starting material. Then, thiophenol (20.5 µl, 0.2 mmol, 1 equivs) is added and stirring at 100 °C is continued until the reaction is complete. The mixture is poured in diethyl ether and washed with water (3 × 100 ml), dried, filtered and evaporated until dryness. The crude product is purified by flash-column (silica, dichloromethane/petroleum ether, 1:1 v/v) to yield the BODIPY (99.5 mg, 80%) as a purple solid. Mp 112 °C. ^{1}H-NMR (600 MHz): δ 8.37 (s, 1H, H-1'), 7.97 (d, *J* = 7.2 Hz, 4H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 4H), 7.05 (m, 2H), 7.04 (t, *J* = 3.0 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 3H), 6.95 (d, *J* = 7.8 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 4.8 Hz, 2H), 6.38 (d, *J* = 4.2 Hz, 2H) ppm; ^{13}C-NMR (150 MHz): δ 171.7, 166.4, 160.2, 128.3, 152.3, 136.1, 135.6, 133.2, 132.4, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.4, 128.0, 126.1, 121. 8, 121.7, 111.7 ppm; LRMS (EI, 70 EV): 622; HRMS: Calculated for $C_{37}H_{25}N_4BF_2SO$ 622.1810, found 622.17992.

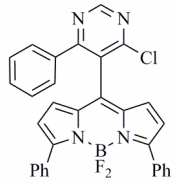
3,5-Diphenyl-8-(4-phenoxy-6-methylsulfanyl-pyrimidin-5-yl)-BODIPY 229e



3,5-Diphenyl-8-dichloropyrimidinyl BODIPY (98 mg, 0.2 mmol) is dissolved in 5 ml of DMF, followed by the addition of phenol (18.8 mg, 0.2 mmol, 1 equivs.), K_2CO_3 (28 mg, 0.2 mmol) and a catalytic amount of 18-crown-6 (2.64 mg, 0.01 mmol, 5%). The mixture is stirred at 100 °C until TLC analysis indicates complete disappearance of the starting material. Then, sodium thiomethoxide (15 mg, 0.2 mmol, 1 equivs) is added and stirring at 100 °C is continued until the reaction is complete. The mixture is

poured in diethyl ether and washed with water (3 × 100 ml), dried, filtered and evaporated until dryness. The crude product is purified by flash-column (silica, dichloromethane/petroleum ether, 1:1 v/v) to yield the desired BODIPY (99.5 mg, 80%) as a purple solid. Mp 106 °C. ^{1}H-NMR (400 MHz): δ 8.69 (s, 1H, H-1'), 7.91 (d, *J* = 7.2 Hz, 4H), 7.46-7.38 (m, 8H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.07 (d, 2H), 6.90 (d, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 4.8 Hz, 2H), 2.57 (s, 3H, -SMe) ppm; ^{13}C-NMR (100 MHz): δ 172.2, 165.9, 160.1, 157.9, 152.4, 135.9, 132.4, 129.9, 129.7, 129.69, 129.65, 129.7, 128.4, 126.0, 121.7, 121.6, 111.8, 13.6 ppm; LRMS (EI, 70 EV): 560; HRMS: Calculated for $C_{32}H_{23}BF_2N_4OS$ 560.16537, found 560.16554.

3,5-Diphenyl-8-(4-Phenyl -6-chloro-pyrimidin-5-yl)-BODIPY 231a



Microwave Suzuki procedure:

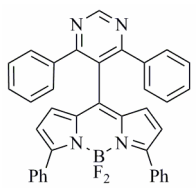
3,5-Diphenyl-8-dichloropyrimidinyl BODIPY (98 mg, 0.2 mmol) is dissolved in DMF (1 ml) and purged with nitrogen. To the resulting solution is added phenylboronic acid (29 mg, 0.26 mmol, 1.3 equivs.), followed by tetrakis(triphenylphosphine) palladium (11 mg, 0.02 mmol, 10 mol%). The mixture is irradiated at 130 °C and 150 W for 15 min, cooled to room temperature and poured in diethyl ether (150 ml). The organic layer is washed with water (3 × 200 ml), dried, filtered and evaporated to dryness. The product is purified by column (silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield monosubstituted product as a purple crystalline solid (67 mg, 63 %), as well as disubstituted BODIPY (17 mg, 15%). Mp of the monosubstituted product: 87 °C

Stille Coupling:

3,5-Diphenyl-8-dichloropyrimidinyl BODIPY (98 mg, 0.2 mmol) is dissolved in toluene (2 ml) and purged with nitrogen. To the resulting solution is added tetraphenyltin (96 mg, 0.22 mmol, 1.1 equivs.), followed by tetrakis(triphenylphosphine) palladium (11 mg, 0.01 mmol, 5 mol%) and Na_2CO_3 (2 ml, 1M solution in H_2O). The mixture is refluxed for 16 h, cooled to room temperature and poured in diethyl ether (150 ml). The organic layer is washed with water (3 × 200 ml), dried, filtered and evaporated to dryness. The product is purified by column (silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield the desired product as a purple crystalline solid (76 mg, 72%). ^{1}H-NMR: δ 9.22 (s, 1H, H-1'), 7.87 (d, *J* = 4.5 Hz, 4H), 7.73 (d, *J* = 6.6 Hz,

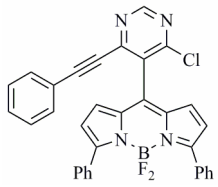
2H), 7.33-7.45 (m, 9H), 6.67 (d, J = 3.3 Hz, 2H), 6.59 (s, 2H) ppm; ^{13}C-NMR: δ 167.0, 162.2, 160.2, 158.9, 136.2, 136.1, 134.8, 132.1, 131.1, 130.1, 129.7, 129.0, 128.9, 128.4, 125.6, 122.1 ppm; LRMS (EI, 70 EV) 532; HRMS: Calculated for $C_{31}H_{20}N_4BF_2Cl$ 532.14376, found 532.14381.

3,5-Diphenyl-8-(4,6-diphenyl-pyrimidin-5-yl)-BODIPY 231b



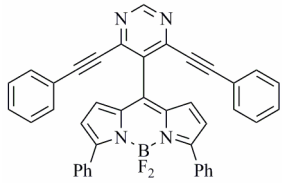
Obtained from the model BODIPY, by using the general procedure for microwave mediated Suzuki reaction. Purple crystalline solid (102 mg, 89%). Mp 140 °C. ^{1}H-NMR: δ 9.51 (s, 1H, H-1'), 7.80 (s, 4H), 7.64 (s, 2H), 7.36 (m, 12H), 6.62 (s, 2H), 6.43 (s, 2H) ppm; ^{13}C-NMR: δ 166.4, 159.1, 159.0, 137.8, 137.5, 136.8, 132.1, 130.2, 129.9, 129.6, 129.4, 128.7, 128.3, 124.4, 121.7 ppm; LRMS (EI, 70 EV) 574; HRMS: Calculated for $C_{37}H_{25}N_4BF_2$ 574.2140, found 574.21.

3,5-Diphenyl-8-(4-phenylethynyl-6-chloro-pyrimidin-5-yl)-BODIPY 231c



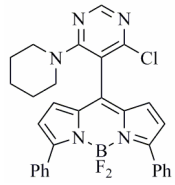
3,5-Diphenyl-8-dichloropyrimidinyl BODIPY (98 mg, 0.2 mmol) is dissolved in THF (2 ml) and iPr$_2$NEt (1 ml) and purged with nitrogen. To the resulting solution is added phenylacetylene (29 µl, 0.26 mmol, 1.3 equivs.), followed by tetrakis(triphenylphosphine) palladium (11 mg, 0.01 mmol, 5 mol%) and CuI (1.9 mg, 0.01 mmol, 5 mol%). The mixture is refluxed for 3 h and cooled to room temperature after which the solvent is stripped. The product is purified by column (silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield the product as a purple crystalline solid (76 mg, 69%). Mp 193 °C. ^{1}H-NMR: δ 9.12 (s, 1H, H-1'), 7.90 (d, J = 4.2 Hz, 4H), 7.43 (s, 6H), 7.34 (m, 3H), 7.26(m, 2H), 6.76 (s, 2H), 6.65 (s, 2H) ppm; ^{13}C-NMR: δ 160.7, 160.6, 159.1, 152.6, 135.7, 133.7, 133.0, 132.2, 130.9, 130.1, 129.6, 129.4, 129.1, 128.7, 128.5, 122.1, 120.2, 102.2 (C≡C), 85.5 (C≡C) ppm; LRMS (EI, 70 EV) 556; HRMS: Calculated for $C_{33}H_{20}N_4BF_2Cl$ 556.1438, found 556.14355.

3,5-Diphenyl-8-(4,6-bis(phenylethynyl*)*-pyrimidin-5-yl)-BODIPY 231d



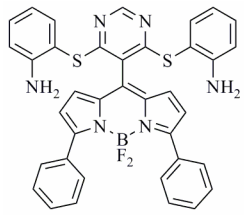
Obtained according to the abovementioned Sonogashira procedure, from the model dye as a purple crystalline solid (69 mg, 56%). Mp 218 °C. ^{1}H-NMR: δ 9.31 (s, 1H, H-1'), 7.92 (d, *J* = 4.5 Hz, 4H), 7.44 (m, 6H), 7.33 (m, 6H), 7.27 (m, 4H), 6.89 (d, *J* = 3.6 Hz, 2H), 6.64 (d, *J* = 2.7 Hz, 2H) ppm; ^{13}C-NMR: δ 160.2, 159.4, 150.9, 136.2, 135.7, 132.9, 132.4, 131.7, 130.6, 130.0, 129.8, 129.6, 128.7, 128.5, 121.9, 120.6, 101.1 (C≡C), 85.9 (C≡C) ppm; LRMS (EI, 70 EV): 622; HRMS: Calculated for $C_{41}H_{25}N_4BF_2$ 622.2140, found 622.21376.

3,5-Diphenyl-8-(4-*N*-piperidinyl-6-chloro-pyrimidin-5-yl)-BODIPY 231e



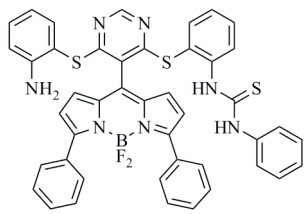
3,5-Diphenyl-8-dichloropyrimidinyl BODIPY (98 mg, 0.2 mmol) is dissolved in toluene (2 ml) and purged with nitrogen. To the resulting solution is added piperidine (13 µl, 0.26 mmol, 1.3 equivs.), followed by trisdibenzylidene acetone dipalladium (18 mg, 0.02 mmol, 10 mol%), BINAP (25 mg, 0.04 mmol, 20 mol%) and KHMDS (30 mg, 0.03 mmol, 1.5 equiv.). The mixture is flushed with nitrogen, and heated at 110 °C in a closed vessel for 1 h. The vessel is cooled to room temperature after which the solvent is stripped. The product is purified by column (silica, CH_2Cl_2/petroleum ether; 1:1, v/v) to yield the desired product as a purple crystalline solid (54 mg, 51%). Mp 200 °C. ^{1}H-NMR (400 MHz): δ 8.48 (s, 1H, H-1'), 7.89 (d, *J* = 4.5 Hz, 4H), 7.43 (m, 6H), 6.88 (d, *J* = 4.28 Hz, 2H), 6.64 (d, *J* = 4.28 Hz, 2H), 3.66(t, 4H, *J* = 5.28 Hz), 1.57 (m, 2H), 1.41 (m, 4H) ppm; ^{13}C-NMR (100 MHz): δ 161.9, 160.7, 159.9, 127.6, 1237.4, 135.9, 132.3, 129.9, 129.7, 129.6, 129.6, 129.2, 128.4, 121.6, 109.0, 48.7, 25.8, 24.5 ppm; LRMS (EI, 70 EV): 622; HRMS: Calculated for $C_{30}H_{25}N_5BClF_2$ 539.1859, found 539.18545.

3,5-Diphenyl-8-(4,6-bis-(*o*-aminophenyl-sulfanyl-pyrimidin-5-yl)-BODIPY 232



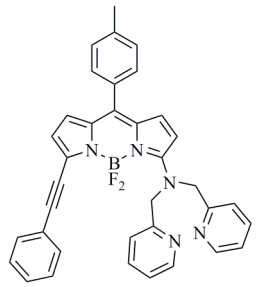
Obtained according to the general procedure for nucleophilic aromatic substitution of the model dye. Mp 144°C; ^{1}H-NMR (400 MHz): δ 8.64 (s, 1H), 7.94 (d, J=5.4 Hz, 4H), 7.45 (m, 6H), 7.30 (d, J = 7.8 Hz, 2H), 7.21 (d, J=7.8 Hz, 2H), 6.93 (d, J=3.6 Hz, 2 H) , 6.75 (, m, 4 H,), 6.70 (d, 3.9, 2H), 4.10 (s, 4H) ppm; ^{13}C-NMR (100 MHz): δ 168.4, 160.1, 158.1, 149.4, 137.8, 135.6, 134.4, 132.3, 132.2, 130.1, 129.7, 128.5, 123.3, 122.1, 119.1, 115.9, 110.9 ppm; LRMS (EI, 70 EV) 668

Thioureum formed from 3,5-diphenyl-8-(4,6-bis-(*o*-aminophenyl-sulfanyl-pyrimidin-5-yl)-BODIPY and phenyl isocyanate 233



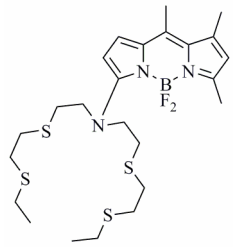
A solution of the *o*-aniline adduct is dissolved (33 mg, 0.5 mmole) is dissolved in toluene (10 ml), phenylisothiocyanate is added, and the mixture is refluxed overnight. The solvent is evaporated and the crude solid is purified chromatographically (Silica; DCM). Mp 145°C; ^{1}H-NMR (600 MHz): δ 8.48 (s, 1H), 8.23 (s, 1H), 8.10 (s, 1H), 7.93 (d, J=6.6 Hz, 4H), 7.90 (d, J=7.2 Hz, 1H), 7.50 (m, 3H), 7.44 (m, 1H, H9), 7.43 (m, 6H), 7.20-730 (m, 5H), 7.14 (m, 1H), 6.81 (d, J=3.0 Hz, 2H), 6.75 (m, 2H), 6.69 (d, J=3.6 Hz), 4.10 (s(br), 2H) ppm; ^{13}C-NMR (150 MHz): δ 180.0, 169.2, 167.5, 160.8, 157.5, 149.5, 141.5, 137.8, 136.8, 136.7, 135.4, 133.3, 132.3, 132.2, 131.5, 130.2, 129.7, 128.7, 128.6, 128.5, 127.7, 127.5, 125.5, 124.0, 122.8, 122.3, 119.1, 115.9, 110.6 ppm; MS (ESI) 803.

4,4-Difluoro-8-(4-methylphenyl)-5-(phenylethynyl)-3-[bis(pyridin-2-ylmethyl)amino]-4-bora-3a,4a-diaza-*s*-indacene 236



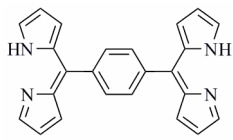
3-Chloro-4,4-difluoro-8-(4-methylphenyl)-5-(phenylethynyl)-4-bora-3a,4a-diaza-*s*-indacene as synthesized following a literature procedure.[53] To a solution of monoacetylene BODIPY(104 mg, 0.25 mmol) in acetonitrile (50 mL) under argon atmosphere was added bis(pyridin-2-ylmethyl)amine (60 mg, 0.30 mmol, 1.2 equivs). The reaction mixture was stirred at room temperature for 16 h. Afterward the resulting solution was poured in water and extracted with dichloromethane (2 × 100 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The crude solid was purified by column chromatography on silica gel using ethyl acetate as eluent to yield 129 mg (89% yield) of a red solid. Mp 176 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.55 (d, 2H, *J* = 4.1 Hz), 7.66 (td, 2H, *J* = 7.9 Hz, *J* = 1.5 Hz), 7.48 (dd, 2H, *J* = 7.9 Hz, *J* = 1.5 Hz), 7.44 (d, 2H, *J* = 7.9 Hz), 7.34 (d, 2H, *J* = 7.9 Hz), 7.28 (m, 3H), 7.24 (d, 2H, *J* = 7.9 Hz), 7.20 (dd, 2H, *J* = 5.3 Hz, *J* = 1.8 Hz), 6.82 (d, 1H, *J* = 4.9 Hz), 6.59 (d, 1H, *J* = 4.1 Hz), 6.36 (d, 1H, *J* = 3.8 Hz), 6.28 (d, 1H, *J* = 5.2 Hz), 5.29 (s, 4H,), 2.42 (s, 3H, tolyl) ppm; ^{13}C NMR ($CDCl_3$) δ 164.2, 156.6, 149.6, 139.2, 137.1, 136.3, 135.4, 133.7, 132.2, 132.0, 131.6, 130.6, 128.2, 128.0, 126.0, 125.6, 123.8, 122.7, 122.1, 120.3, 119.5, 115.3, 100.1, 95.6, 84.0, 58.1, 22.8 ppm; IR (cm^{-1}) 3055 (m), 3014 (m), 2920 and 2852 (CH_2, s), 2202 (C≡C, w); LRMS (EI, 70 eV) m/z 579; HRMS: calculated for $C_{36}H_{28}BF_2N_5$ 579.2406, found 579.23967.

4,4-Difluoro-5,7,8-trimethyl-3-[bis(2-(2-(ethylthio)ethylthio)ethyl)amino] -4-bora-3a,4a-diaza-*s*-indacene 239



Obtained according to the general procedure for nucleophilic substitution of a monohalogenated BODIPY dye. Red solid; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, 1H, J = 4.8 Hz), 6.04 (d, 1H, J = 5 Hz), 5.95 (s, 1H), 3.88 (t, 4H, J = 7.52 Hz), 2.86-2.80 (m, 8H), 2.76-2.72 (m, 4H), 2.56 (q, 2H, J = 14.88 Hz, J = 7.32 Hz), 2.45 (s, 3H), 2.43 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 159.4, 146.7, 133.7, 133.0, 131.8, 130.1, 129.2, 118.6, 1092, 53.3, 32.2, 31.9, 30.0, 29.7, 26.0, 16.1, 15.8, 14.7 ppm; LRMS (EI, 70 EV): 545; HRMS: Calculated for $C_{24}H_{38}BF_2N_3S_4$: 545.2010, found 545.2023.

General procedure for the deborylation of BODIPY dyes in acidic environment: *bis* dipyrrin 250



A BODIPY dye is dissolved in a mixture of acetonitrille and HCl (37%) ((9:1 v/v), 0.2 M solution) and the resulting mixture is stirred at 60°C for 3 hours, or until all starting compound has disappeared. The solution is poured in acidified water, and extracted with diethyl ether to remove any traces of organic side products. The water layer is then basified with concentrated NaOH (aq.), and the dipyrrin is extracted into diethyl ether (2 x). The organic layer is subsequently washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness to yield the dipyrrin as a virtually pure solid. Bright orange crystalline solid; Mp 119°C (Decomposition); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.67(m, 4H), 7.58 (m, 4H), 6.67 (d, 4H, J = 4.04 Hz), 6.43 (q, 4H, J = 1.28 Hz, J = 4.04 Hz) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 143.8, 141.0, 140.8, 137.9, 130.0, 128.6, 117.8 ppm; LRMS (EI, 70 EV): 362; HRMS: Calculated for $C_{24}H_{18}N_4$ 362.1531, found 362.15062.

6. List of Publications

Synthesis, Spectroscopy, Crystal Structure, Electrochemistry, and Quantum Chemical and Molecular Dynamics Calculations of a 3-Anilino Difluoroboron Dipyrromethene Dye; Qin Wenwu, Leen Volker, Rohand Taoufik, Dehaen Wim, Dedecker Peter, Van der Auweraer Mark, Robeyns Koen, Van Meervelt Luc, Beljonne David, Van Averbeke Bernard, Clifford John N, Driesen Kris, Binnemans Koen, Boens Noël; **2009**; *Journal of Physical Chemistry A;* 113; 2; 439-447.

A versatile, modular synthesis of monofunctionalized BODIPY dyes; Leen Volker, Braeken Els, Luckermans Kristof, Jackers Carine, Van der Auweraer Mark, Boens Noël, Dehaen Wim; **2009**; *Chemical Communications;* 30; 4515-4517.

Synthesis and Substitution of 8-(4,6-Dichloropyrimidin-5-yl)-BODIPY; Leen Volker, Schevenels Florian, Cui Jie, Xu Chan, Yang Wensheng, Tang Xiaoliang, Liu Weisheng, Qin Wenwu, De Borggraeve Wim, Boens Noël, Dehaen Wim; **2009**; *European Journal of Organic Chemistry;* 34; 5920-5926.

3,5-Dianilino Substituted Difluoroboron Dipyrromethene: Synthesis, Spectroscopy, Photophysics, Crystal Structure, Electrochemistry, and Quantum-Chemical Calculations; Qin Wenwu, Leen Volker, Dehaen Wim, Cui Jie, Xu Chan, Tang Xiaoliang, Liu Weisheng, Rohand Taoufik, Beljonne David, Van Averbeke Bernard, Clifford John N, Driesen Kris, Binnemans Koen, Van der Auweraer Mark, Boens Noël; **2009**; *Journal of Physical Chemistry C;* 113; 27; 11731-11740.

Synthesis and photophysical characterization of chalcogen substituted BODIPY dyes; Fron Eduard, Coutino-Gonzalez Eduardo, Pandey Lesley, Sliwa Michel, Van der Auweraer Mark, De Schryver Frans, Thomas Joice, Dong Zeyuan, Leen Volker, Smet Mario, Dehaen Wim, Vosch Tom; **2009**; *New Journal of Chemistry;* 33; 7; 1490-1496.

Synthesis, Spectroscopy, Crystal Structure Determination and Quantum Chemical Calculations of BODIPY Dyes with Increasing Conformational Restriction and Concomitant Red-Shifted Visible Absorption and Fluorescence Spectra; Leen Volker, Qin Wenwu, Yang Wensheng, Cui Jie, Xu Chan, Tang Xiaoliang, Liu Weisheng, Robeyns Koen, Van Meervelt Luc, Beljonne David, Lazzaroni Roberto, Tonnelé Claire, Boens Noël, Dehaen Wim; **2010**; *Chemistry, An Asian Journal* (*Accepted)*.

Direct functionalization of BODIPY dyes by oxidative nucleophilic hydrogen substitution at the 3- or 3,5-positions; Leen Volker, Zaragozí Gonzalvo Verónica, Deborggraeve Wim M., Boens Noël, Dehaen Wim*;* **2010***; Submitted*.

Synthesis, Crystal Structure, Electrochemistry, Solvatochromism and Metal Ion Complex Formation of A Ratiometric, Fluorescent BODIPY-Based Probe with Di-(2-picolyl)amine Chelator, Yang Wensheng, Leen Volker, Dehaen Wim, Van der Auweraer Mark, Xu Chan, Cui Jie, Dou Wei, Liu Weisheng, Qin Wenwu, Boens Noël, **2010**, *Submitted*.

Synthesis and substitution of monohalogenated BODIPY dyes: correlating synthesis, structure and spectroscopy; Leen Volker, Deborggraeve Wim M., Boens Noël, Dehaen Wim, **2010**, *Manuscript in preparation*.

Vicarious substitution of hydrogen on BODIPY dyes; Leen Volker, Deborggraeve Wim M., Boens Noël, Dehaen Wim, **2010**, *Manuscript in preparation*.

Synthesis and substitution of 1,7 dihalogenated BODIPY dyes; Leen Volker, Deborggraeve Wim M., Boens Noël, Dehaen Wim, **2010**, *Manuscript in preparation*.